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Contents

I have been asked as an expert in drug labeling and FDA regulation to provide opinions, based on my training, experience and expertise, with respect to Food and Drug Administration (FDA) regulation of the development, approval, and marketing of pharmaceutical products in the United States, as well as FDA requirements for preclinical and clinical studies, Investigational New Drug applications, New Drug Applications, labeling, post-marketing surveillance, pharmacovigilance, and monitoring of adverse event reports. I have also been asked as an expert in clinical epidemiology to provide opinions regarding the epidemiologic evidence regarding hormonal contraceptives and idiopathic intracranial hypertension.

I. Qualifications

I serve as an expert consultant on regulatory matters under the jurisdiction of the United States Food and Drug Administration (FDA), as an expert clinical epidemiologist, and on matters related to pharmaceutical products, the pharmaceutical industry, and other areas within my expertise, as described below.

I am board certified in Internal Medicine and have a Master's Degree in Public Health in the fields of epidemiology and biostatistics. I graduated from Stanford University Medical School in 1976; completed my internship and residency at the University of California, Davis in 1979; and earned an M.P.H. from the University of California, Berkeley in 1983. I was an Andrew Mellon Scholar in Clinical Epidemiology at the University of California, San Francisco from 1982-1984.

From 1982-1989, I held several positions at the University of California, San Francisco, including Associate Director of the Clinical Epidemiology program and Assistant Professor of Medicine with joint appointments in Epidemiology and Biostatistics, and was a member of the Pharmacology faculty. I was also Director of the Data Center at the AIDS Clinical Research Center. From 1989 to 1991, I was a Clinical Associate Professor of Clinical Medicine at the University of California, San Diego.

During my career, I have practiced medicine as a general internist in faculty practices at the University of California, as well as taught medical students, interns, residents, and fellows, and cared for patients on the in-patient services at several university hospitals. As an internist-epidemiologist, I conducted original research on risk factors for disease, including case-control and cohort studies, and designed and conducted clinical trials. My responsibilities for clinical trials included monitoring and reporting adverse drug reactions to FDA and to the trials' data

safety and monitoring boards, as well as to Institutional Review Boards (IRBs). Clinical trials that I designed and conducted led to the approval of new drugs and devices. I presented to and served on FDA Advisory Committees, as well as National Institutes of Health and Public Health Service Consensus Task Forces on disease prevention and treatment that included evaluation of the quality of evidence from epidemiology and clinical trials.

From 1992 to 2004, I held a number of senior positions at FDA. From 1992-1997, I held positions in FDA's Center for Drug Evaluation and Research (CDER). This Center has the responsibility for the review and approval of all new drugs, and the ongoing assessment of the quality, safety and effectiveness of marketed drugs. It has the authority to take actions through its compliance programs to assure that drugs meet standards defined in law. At CDER, I held the positions of Director of the Division of Anti-Viral Drug Products and Acting Director of the Anti-Infective Drug Products, and in addition from 1994 to 1997, I was Director of the Office of Drug Evaluation IV. When I was Director of the Anti-Viral Drug Products Division, I was responsible for drugs to treat such conditions as AIDS, herpes, hepatitis, influenza, serious fungal diseases, and tuberculosis. While I was the Acting Director of the Anti-Infective Division, I was responsible for drugs to treat bacterial infections, such as urinary tract infections, pneumonia, skin infections, and others.

I had the direct authority to approve investigational studies of new drugs for these indications, to halt such studies for safety reasons, to approve new indications for approved drugs in these areas, and to approve the manufacturing methods and take compliance actions through the CDER Office of Compliance and FDA field staff. My responsibilities included the review and approval of product labeling, in particular, indications and safety warnings for hundreds of labeling changes. Safety reviews included evaluation of animal studies, clinical trials, signal detection systems such as MedWatch, case-control studies and registries. As an Office Director, I supervised the directors of these two Divisions and was one of five people at FDA with the authority for the initial approval of new drugs. I also shared responsibility for policy development including drafting FDA Guidance documents.

From 1997-1999, I served as the Medical Deputy Director of the Center for Biologics Evaluation and Research (CBER). In this position, I was responsible for medical issues arising with blood, vaccines, and therapeutic proteins, such as interferon or erythropoietin. I directly supervised the Biostatistics and Epidemiology Division, among others, as well as the Advisory Committee Staff and served as the Center Ombudsman.

From 1999-2004, I served as Director of the Center for Devices and Radiological Health (CDRH). This Center is responsible for medical devices ranging from x-ray equipment, surgical

equipment, implants, pacemakers, orthopedic products, as well as consumer products, such as microwave ovens and cell phones. The Offices that were responsible for approval of new devices, safety surveillance, and compliance were among those that reported to me. I was directly involved in evaluating significant new potential safety problems that could result in changes in product labeling, risk management plan or product withdrawal. Like CDER and CBER, this Center has the authority to require labeling changes and other actions when products have safety problems or do not meet standards of manufacturing quality.

My career has included extensive experience in the evaluation of safety and effectiveness of pharmaceuticals, as well as other therapeutic modalities. At FDA, I was responsible for the evaluation of safety and efficacy of new drugs, including the approval process and continuing oversight of the safety and effectiveness of those drugs after approval. This involved extensive interactions with sponsors about their study design and product development programs, evaluating the results of those programs and product labeling. As a Division Director and Office Director, I had direct responsibility for evaluating the adequacy of the preclinical and clinical studies that were the basis for New Drug Applications (NDAs), and I had direct sign-off authority, known as "signatory authority," for their approval. In addition to direct review of applications, I participated in policy and guidance efforts at FDA to develop standards for review of drug safety, including drafting the current FDA Guidance for reviewers on how to review the safety section of an NDA. I presented safety evaluations to the Committee of the Institute of Medicine, in congressional testimony, and published invited commentaries on product safety. I understand fully the process and criteria utilized by FDA in assessing safety and efficacy, pharmaceutical product labeling and pharmaceutical manufacturing quality, and I participated directly in that process for years.

Since leaving FDA, I have taught and participated in research grants at Arizona State University (ASU), where I am currently an Adjunct Professor in the School of Law; I have taught a course on Food and Drug Law for the last eight years. In the research area, I have assisted my colleagues in the Biodesign Institute at ASU in developing a scientifically sound regulatory path for products ranging from diagnostic tests to detect radiation exposure, as part of federally funded counter-terrorism efforts, to artificial limbs with sensors that would allow a prosthetic hand or foot to "feel" what it touches and communicate that wirelessly to peripheral nerves. I have also assisted start-up medical product companies develop research plans that will comply with the high FDA standards.

I have also held two senior positions in two biotech-pharmaceutical companies. At Élan Pharmaceuticals, I was the Senior Vice President for Global Regulatory, Global Safety and Biostatistics. Our research and development team successfully obtained approval from FDA for

a new drug to treat Crohn's Disease during that time period. At Amgen, as the Vice President for Global Regulatory, product labeling was a nearly daily part of my job.

As a consultant in legal cases over the last eleven years, I have provided expert review for both defense and plaintiffs' attorneys. This consulting has usually involved expert review of topics, including assessment of company and FDA processes in the development of new drugs, the detection of signals of potential new adverse events, the adequacy of product safety labeling, the process of revising and keeping product labeling up to date, manufacturing quality requirements for new drug approval, the regulatory basis for market approval for drugs and devices, off-label use, FDA enforcement activities and the scientific basis for regulatory decisions by FDA, the explanation and application of principles and concepts of epidemiology and biostatistics, and other topics.

A copy of my curriculum vitae, including a list of publications that I have authored, and a list of documents I have reviewed in preparing this statement are attached as Exhibits A and B . My previous testimony in trials and depositions, in the last four years is attached as Exhibit C.

I am being compensated in this case at the rate of $600/hour.

In forming my opinions, I have relied on my knowledge of FDA regulations, policies, review procedures, and practices, as well as my training and experience as a physician and an epidemiologist. All of the opinions stated in this report are expressed to a reasonable degree of scientific and medical certainty.

II. FDA Requirements and Review Practices

A. FDA's Regulatory Role

The FDA is a 100-year-old consumer protection agency with enforceable legal authority to assure that drugs are safe and effective, properly manufactured, and that the drug's benefits outweigh its risks for intended use. Congress vested FDA with the sole authority to approve drugs for commercial use and to withdraw that approval, if appropriate. The FDA requirements are specified in law by the Food Drug & Cosmetic Act (FDCA) passed by the U.S. Congress. The requirements of the law are described in detail in the Code of Federal Regulations. The Agency regulates and monitors the study, manufacturing, labeling, distribution, and postmarket surveillance of all prescription drugs within the United States. FDA primarily performs these tasks through the Center for Drug Evaluation and Research (CDER), one of the world's largest

drug regulatory agencies. CDER is organized into Offices, which are divided into Divisions, which specialize in drug development areas, such as manufacturing, development of new drugs, and postmarket surveillance.

Regulations have the same binding force as the law itself and failure of a product to meet these standards is a violation of the law with specified penalties. FDA also provides non-binding advice through Guidance documents. These public documents provide FDA's perspective on the whole range of issues that FDA regulates from study design to manufacturing. The recommendations are neither binding nor a guarantee of success, but represent FDA's current thinking on a given topic.

B. The New Drug Approval Process

1. Investigational New Drugs – The Phases of Drug Development

Prior to introducing a new pharmaceutical compound to the U.S. market, FDA requires every pharmaceutical company to first submit an Investigational New Drug application (IND) to the Agency. This application provides FDA with data on the manufacture of the drug, animal studies demonstrating its safety, *in vitro* studies, and protocols for future studies on human participants. If FDA accepts the IND application based on these studies, the product then undergoes clinical trials to establish safety and effectiveness in humans. In the IND phase of development, FDA has the authority to place a hold on further development of a drug product if the safety of the drug is in question. The foremost consideration for FDA during clinical investigations is drug safety. Patients in the clinical trials done under an IND are monitored to detect adverse effects. Because not all adverse effects can be anticipated, the tests are designed to assess drug effects on many different body systems. FDA meets regularly with sponsors throughout the IND process. Topics commonly discussed include dose, duration, endpoints, patient populations, comparator drugs and trial design for testing in humans.

It takes many clinical trials to provide the evidence that a drug is safe and effective for an intended use for a specific patient population. FDA regulations describe these trials in three phases, from the first small trials in normal volunteers, to the larger trials in specific patient populations, to the still larger adequate and well-controlled trials that confirm that a drug is safe and effective. Phase 1 trials are small closely monitored studies, usually in normal volunteers, to learn how a drug is absorbed and eliminated from the body and to determine safe doses for further testing. Typically, fewer than 100 subjects participate in Phase 1. Phase 2 trials are the first trials to evaluate the effectiveness of the drug for patients with a particular condition. These studies often involve several hundred patients. They are used to learn enough

about the drug to plan the larger trials in Phase 3 that will study the safety and effectiveness of the drug for one or more indications. All of these trials provide the basis for a New Drug Application (NDA) and may involve several thousand study participants. The phases frequently overlap. The process of studying a new drug is iterative as new information is learned about safety and effectiveness on an ongoing basis. Lack of effectiveness or safety problems are common and fewer than 15% of all drugs which start in Phase 1 testing complete the clinical trial process and are approved for marketing.

2. New Drug Application Review – Evaluating Safety, Effectiveness and Benefit / Risk

a. The Review Process

Following the IND phase, the drug product's sponsor submits to FDA an NDA containing data it has gathered on the product's safety and effectiveness. Generally, the NDA contains the following information: (i) reports of preclinical and clinical studies; (ii) a summary of all safety data; (iii) pharmacological data on the drug's composition; (iv) methods and facilities used in the drug's manufacturing; (v) samples of the product; and (vi) proposed labeling. These requirements are set out in detail in the regulations found at 21 CFR § 314.50.

When an NDA is received, FDA will decide if the application will be reviewed as a priority review or standard review. Even before the User Fee Act was passed by Congress in 1992, FDA assigned target review decision dates for priority review products at six months rather than the twelve month standard targets. To accomplish the faster review with the same degree of rigor, FDA expands the size of the team reviewing the product, and schedules Advisory Committee Meetings and manufacturing inspections at an earlier time point. Review decision dates are not targets for making a final decision. Rather, they are the time when a manufacturer can expect a "complete review" of the application, and while the application may be approved after a complete review, it is more common for FDA to identify additional information, called application "deficiencies," that must be addressed before a final decision is made.

FDA employs a number of resources in reviewing the NDA data, including a team of physicians and other scientists, who are experts in their respective fields. This team prepares detailed reports in their area of expertise based on their findings. These reviews and reports may contain conclusions and recommendations of the individual reviewers at the time they are written, but do not necessarily represent the final FDA position. During the review process, FDA has complete access to all of the data from the studies in the NDA, either as submitted at the time of filing or per FDA's request to the NDA applicant.

Typically, FDA and the applicant have many communications back-and-forth during FDA's review so the sponsor has an opportunity to address questions and issues identified by FDA during its review. FDA determines whether the information submitted in the NDA is sufficient to establish that the drug meets FDA's effectiveness and safety requirements. FDA will request specific information and analyses during the review that it deems necessary. When the drug passes this rigorous review, FDA will issue a letter to the drug sponsor approving the NDA. However, if FDA concludes that the application is incomplete or if questions remain to be answered, FDA will issue a letter outlining any deficiencies or faults in the application. Until 2006, the letter indicated whether FDA concluded that the application was "approvable" with the additional information, or whether it found that the application was currently "nonapprovable" because of more significant issues.[1]

The ultimate purpose of the review of the preclinical and clinical data within the NDA is for FDA to review and ultimately approve the product with a label that provides adequate instructions for the safe and effective use of the drug for the purposes indicated. The format, content, and organization of the product label are specified by FDA in the regulations in order to assure uniformity and clarity. While the contents of the label are initially the result of discussion between the sponsor and FDA, FDA makes the final determination. Even following the drug's approval and release on the market, the labeling is continually reviewed by FDA for possible revisions based on postmarketing safety data and other information provided by the company and other sources available to FDA. The current labeling regulations were promulgated in 1975 and reiterated in 2006.

FDA recognizes that advances in medical knowledge precede labeling revisions by manufacturers and formal FDA labeling approval. As FDA has noted, in addition to labeling, other sources of information are essential to proper use of drugs:

> Physicians clearly have access to new information on drugs through the medical literature, scientific meetings, postgraduate courses, and professional contacts with colleagues. The package insert is not intended under the law to serve as a totally current repository of all such information. It is intended instead to be an authoritative document which contains only those indications and usages based upon substantial evidence of safety and effectiveness. [3]

[1] FDA's current practice is to call letters "Complete Response" letters, which list the application's deficiencies, or "Approval Actions."

b. FDA NDA Decisions

When FDA makes a final determination that the sponsor's drug is safe and effective and has appropriate labeling, it will approve the NDA. The NDA approval means that FDA determined that, for the intended use, the sponsored product's benefits outweigh any known risks that may occur when the product is used in accordance with the approved labeling. This risk-benefit assessment is conducted with every FDA-approved drug on the market and is a crucial element of the drug approval process. This process of risk-benefit assessment occurs throughout the life of the drug, including each time FDA approves a change in the product for a new indication or approves a modification of a safety section of the product label. As part of the approval process, FDA drafts reviews documenting the evidence it considered and the reason for its decision. At the time of approval, as described in FDA approval letters, postmarketing commitments and requirements are described, many times to add additional evidence to the safety information available at the time of approval and to overcome the limitations of postmarketing surveillance, described below.

C. Marketed Products: Phase 4 and Postmarketing Safety Surveillance

Following a new drug approval, the manufacturer begins the next phase of drug development, the postmarketing period or Phase 4, when the drug is available for prescription use. To describe safety in the initial labeling, FDA rigorously compares the detailed safety information from the premarket clinical trials participants to the trials' control groups, allowing the comparison of adverse effects in patients who took the drug to those who did not. Once the drug is on the market, the number of patients who take the drug expands from the few hundreds or thousands of patients in the clinical trials, to tens of thousands or even millions of patients who are prescribed the drug by their physicians. The manufacturer of the drug reports the findings from the marketed experience to FDA in several ways, as described below.

1. Spontaneous Adverse Event Reports

Premarket safety studies will not detect all of the adverse effects related to the drug because the testing is conducted in a limited number of patients and because the types of patients are more diverse in marketed experience than in clinical trials. For these reasons, manufacturers are required to continue to collect and report adverse experience information after approval. [18] This postmarketing surveillance includes spontaneous reports of individual cases from healthcare practitioners, patients, and others, foreign adverse experience reports, new clinical trials, and information from the medical literature.

Spontaneous postmarketing adverse event reports must identify, at least: 1) the adverse event(s); 2) possible suspect drug(s); 3) a specific patient; and 4) the source of the report. There are limitations to spontaneous reports which must be taken into account. For example, patients may have multiple medical problems, they may have taken many different medications, and the reports often have incomplete information and lack follow-up information.

FDA specifies in its regulations when and how to report adverse events, with a particular focus on reporting "serious" and "unexpected" events, terms defined by FDA regulations. [18] These events are to be reported to FDA within 15 days of receipt by the manufacturer. Manufacturers submit other reports in periodic and annual reports. The regulations specify that periodic reporting does not apply to the medical literature or to foreign reports that are not subject to 15-day reporting requirements. [18]

The manufacturers, as well as two groups within FDA, analyze spontaneous adverse event reports as they are received. The physicians, epidemiologists and other scientists in the Office of Surveillance of Epidemiology code, process, and evaluate spontaneous reports.[2] At the same time, the multidisciplinary review team within the New Drug division which has overall responsibility for the drug and its labeling, independently evaluates safety information, and, with respect to labeling, focuses on the 15-day spontaneous adverse event reports.

During the first several years of marketing, periodic safety report summaries are required every three months. Serious and unexpected spontaneous reports must be filed with FDA within 15 days. In particular, FDA closely follows new drugs to identify potential adverse events that had not previously been recognized, or to gather additional information about potential issues which had been identified in the premarket period.

The purpose of spontaneous reporting systems is to detect a "signal" of a previously unknown potential association between an adverse effect and a drug. Beyond examining individual spontaneous reports, signal evaluation may include epidemiological studies, research on the pathophysiology of the adverse reaction, and, where feasible, clinical trials.

2. Phase 4 studies and controlled trials for new indications

Another important source of safety information comes from clinical trials and other studies conducted after the initial market approval. Some of these studies, referred to as "Phase 4

[2] The FDA adverse event report database, FAERS (formerly AERS and before that SRS) is available to the public. The coded sections of the reports are available quarterly for download; the narrative portion of the report is available by Freedom of Information Act (FOIA) request.

Postmarketing Commitments," are studies that the company agrees to conduct after marketing to provide additional information about specific issues that were identified in the NDA review, but were not thought to be necessary to conduct prior to NDA approval. FDA also has the authority to require safety studies in the postmarketing period.[3]

It is common to study new formulations or new uses of the drug after initial approval. These new uses require new Phase 2 and Phase 3 controlled trials and often add substantially to the safety database. The results of these studies are submitted to FDA as Supplemental NDAs, ("Efficacy Supplements" or "Safety Labeling Supplements"). These supplements are reviewed with the same rigorous standards as the original NDA by FDA staff to assure that the risk-benefit assessment for the drug indicates that the drug is safe and effective for the newly proposed and existing intended uses. Through this process FDA assures that the label remains accurate and up to date.

3. Additional sources of information

It is important to note that FDA has sources of information not available to any single manufacturer. In addition to spontaneous reports sent directly to FDA, drug development programs of one manufacturer may contain detailed studies of another manufacturer's drug used as a control group.

4. Medical Literature

Once a new drug is available on the market, additional studies will often be conducted by independent investigators. In addition to clinical trials, there are also publications of individual patients or a series of patients thought to have had adverse experiences from a drug or from related drugs. Independent investigations are also published describing drug interactions or reports of the experience using the drug in special populations, such as children, the elderly, patients with unapproved indications, or in patient groups who were not included in pre-approval studies due to the application of inclusion or exclusion criteria. The FDA staff and the product's manufacturers monitor the literature databases for new information, in particular about safety. It is well-known and understood that additional information about the benefits and risks of medicines will become available after they are approved, and that evaluation of that information is an ongoing process.

[3] FDCA 505(o)(3).

5. Clinical Trials, Epidemiology and the Hierarchy of Evidence

As scientific evidence of safety is of varying degrees of reliability, accuracy, and validity, there is a recognized hierarchy of evidence for scientific evidence relevant to the assessment of drug safety, as described in the table below.

Among the important features of drug safety evidence to consider are: 1) whether the evidence was collected prospectively or retrospectively;[4] 2) whether the spectrum of the adverse events observed are representative; 3) the background rate of the adverse event not associated with drug use; 4) the background rate of use of the drug in the relevant population; 5) whether there are relevant control groups; and 6) whether the study execution was thorough and unbiased.

Adverse reactions that occur in at least 0.5% of patients are usually detected in the clinical trials and described in the product labeling at product approval. Infrequent and rare adverse reactions are often described initially by individual case reports, either reported to the company or FDA, or published in the medical literature as a case series after the product enters the market. When performed properly, case-control studies are the best method to determine whether there is an increased risk of infrequent adverse events associated with a drug. When both the drug use is infrequent and the adverse event is rare, the very large pharmacoepidemiology databases[5] may be the only practical method to assess risk.

[4] I.e., did the study start when a drug is started with follow-up to detect adverse effects, or did the study start with the adverse effect and then look back to see what drugs had been taken.

[5] Through the 1990s, databases of insurance records for payment for prescriptions and diagnosis codes for healthcare were available for populations of several hundred thousand patients. Now, country-wide databases from Europe, Medicare databases in the U.S., and large insurance databases provide the ability to study as many as 100 million patients.

Hierarchy of Study Design and Evidence for Drug-Associated Adverse Effects				
Hierarchy of Designs (Strongest to Weakest)	**Adverse Effects assessed prospectively before adverse event?**	**Controls for Selection Bias / and Ascertainment Bias?**	**Can estimate relative risk or hazard compared to control group?**	**Can study rare events?**
Randomized Controlled Trials (enroll patients who are randomized into groups and who take a new drug or placebo or other control)	Yes	Yes	Yes	No
Controlled Cohort Studies (enroll patients starting a new drug and compare to similar patients not taking the drug)	Yes	No / Maybe	Yes	Maybe
Registries and other uncontrolled cohort studies (e.g., pregnancy registries)	Yes	No / Maybe	No[6]	No
Case – Control Studies (enroll patients who have already had an adverse effect and compare to similar patients without the adverse effect and look	No	Maybe / Maybe	Yes	Yes

[6] When events, such as certain birth defects, are known to occur at certain rates, a birth defect registry can estimate whether there is likely to be an increased risk.

back to see drug use)				
Pharmacoepidemiology Studies (cohort or case-control designs conducted with insurance databases)	Yes / No	Maybe / Maybe	Yes	Yes
Case Series (a collection of patients with an adverse event)	No	Maybe / No	No	Yes
Individual Case Reports (report of a single patients with an adverse event associated with a drug)	No	No / No	No	Yes

6. Spontaneous Case Reports

An individual spontaneous case report is the observation of an adverse event associated with a drug. These reports may be useful in some cases to detect signals of a potential association between outcomes and medical treatments. The FDA and product manufacturers use spontaneous reports to detect new potential safety issues. These reports, even when aggregated, cannot provide estimates of incidence rates or prevalence for the product, let alone provide comparative rates between products. [33][7]

As FDA has recognized in a Guidance document on pharmacovigilance, it is "rarely possible to know with a high level of certainty" whether an event reported in an individual case report was caused by the product. Only in extraordinary circumstances can a single spontaneous report result in a labeling change, usually for adverse events which do not occur in the absence of drug exposure. According to FDA, "Rigorous pharmacoepidemiologic studies, such as case-control studies and cohort studies with appropriate follow-up, are usually employed to further examine the potential association between a product and an adverse event." [33] FDA has made clear that

> FAERS data do have limitations. First, there is no certainty that the reported (adverse event or medication error) event was actually due to the product. FDA does not require that a causal relationship between a product and event be

[7] At best, the number of spontaneous reports can be compared to market share or total sales, but since many factors, including publicity, stimulate reporting, these estimates may not be reliable.

> proven, and reports do not always contain enough detail to properly evaluate an event. Further, FDA does not receive reports for every adverse event or medication error that occur with a product. Many factors can influence whether or not an event will be reported, such as the time a product has been marketed and publicity about an event. Therefore, FAERS data cannot be used to calculate the incidence of an adverse event or medication error in the U.S. population. [58]

Reporting of adverse events by physicians and patients is both voluntary and spontaneous. Recent data suggest that reporting rates can vary widely based on a number of factors, including publicity surrounding a drug adverse event, litigation, or a recall, extent of use in the population, and marketing of a drug. There has been an increase in adverse event reporting rates over recent years. [45]

Data Mining: Beginning in the late 1990's, FDA and others have studied statistical techniques to identify events reported more frequently in association with specific drugs. [28, 30, 34, 36, 68, 77] Szarfman, A., et al. [28], estimated in 2002 that there were greater than 40,000 "signals" identified, even with a method that adjusts for drug-event pairs with a small number of reports. With these methods, any given drug-event report out of the 10.4 million drug-event associations had a 23% chance of being a signal. Szarfman, went on to comment:

> The validation of data mining in an absolute sense is an unreachable goal. There is no true gold standard for every adverse drug event against which the data mining systematic results can be linked and compared.[8]

Various methods to identify signals by detecting relatively higher reporting rates have been developed and compared. [34, 36] As a group, these methods are called disproportionality analyses, and all of them assess differences in adverse event reporting behavior that, like the individual cases that they are based upon, cannot establish a causal relationship between an event and a drug.

The most naïve approach, the Proportional Reporting Rate (PRR) and the related statistic the Proportional Odds Ratio, is to compare the proportion of reports for a single drug-event association to all reported drug-event associations. Without stratification, or comparison between drugs with similar use, it assumes that the patient population for the single drug-event pair is the same for the use of all drugs. Such methods will spuriously detect signals for diseases of the elderly when a drug-event association used in the elderly is compared to all drug-event pairs used across all ages.

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[8] *See* page 387.

A more fundamental problem with the PRR[9] is signal exaggeration for drug event pairs with a small number of events. Levine, J.G., et al. [36] points out that using the AERS database, the PRR classifies more than half of all drug-event association pairs as a signal for 90% of all drugs in the first year they are on the market, "regardless of the clinical plausibility."[10] FDA has been a proponent of methodology that adjusts for this effect, with methods that both take into account the distributional properties of rare events (the Poisson distribution) and model the likelihood of reports for a given pair empirically from the reporting characteristics of other pairs to adjust the probability (Bayesian methods). The most widely used method by FDA authors is the Multi-item Gamma Poisson Shrinker (MGPS) [26], but as FDA points out even this method only identifies differences in reporting rates and

> To further study the adverse-event risk, the signals generated by MGPS can be evaluated by individual case review and compared with various analyses from other sources (e.g. clinical trials, general practice databases, literature reports).[11]

7. Role of FDA in the Postmarketing Period

FDA remains vigilant about drug safety throughout the lifecycle of a drug. The FDA postmarketing surveillance standards are robust: FDA requires manufacturers to have organized systems to detect, assess, and follow-up safety issues and FDA inspects and audits company clinical trials and postmarketing surveillance systems to assure the integrity of the process. When FDA scientists raise questions about a specific issue, they will ask manufacturers to provide additional information about that issue, and may require modification of the product's labeling and take other actions to communicate the new information to prescribing healthcare professionals. While a manufacturer only has access to its own data, FDA has access to data from all manufacturers relating to the drug, which can often provide important adverse event information.

In parallel to FDA field inspectors examining on-site study records from clinical trials, FDA regularly inspects manufacturers' pharmacovigilance operations, verifying the accuracy and timeliness of the systems in place to collect, analyze, and report spontaneous adverse events. Most of the inspections are unannounced and routine, but when there is an important new safety issue, it is not uncommon for FDA to conduct a pharmacovigilance inspection or to visit

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[9] Whether the comparison is of relative proportions or relative odds (odds ratios).

[10] *See* page 106. The authors go on to comment: "Even in the cases when the event appears in the product labeling, many factors other than a true causal relationship between a drug and an event may influence the labeling, such as some class effects, litigation and publicity."

[11] *See* page 7.

clinical sites where there are a number of reports. As with all inspections, FDA presents a list of potential violations to the company at the end of the inspection, a 483 form, and after review of those observations, FDA will write up an Establishment Inspection Report (EIR), which will lead to a finding that no actions are needed or that voluntary or mandatory actions are required. When FDA identifies serious findings of potential violations, it may issue a Warning Letter.

D. Product Labeling

Professional product labeling is a highly regulated monograph that, for a given product, describes in detail FDA-approved indications for use, the clinical pharmacology and efficacy determined from adequate and well controlled studies, and safety from multiple sources, including controlled studies and postmarketing surveillance. Labeling is the key source of information to assure safe use.

A label provides physicians with a clear and concise summary of the information necessary for the safe and effective use of the drug. As such, prescription drug labeling is directed to healthcare professionals and not to consumers. An FDA-approved label is a summary of the essential scientific information, providing an evidence-based assessment of risk and benefit for specific indications, to assist a prescriber making decisions for individual patients. Accordingly, the label is not intended to be an encyclopedia of all possible information and theories about benefits and risks, or to provide a text book of medicine about the disease treated or particular adverse reactions. In addition, the label directly affects what may lawfully be included in drug promotion and advertising.

FDA has clearly communicated that labels are to be based on evidence, commenting that "theoretical hazards not well-grounded in scientific evidence can cause meaningful risk information to 'lose its significance.'"[37][12] FDA recognizes that over-warning about potential risks can have a negative effect on patient safety and public health. In the 2006 update on labeling requirements, FDA stated:

> [R]equirements for the disclosure of risk information are not necessarily more protective of patients. Instead, they can erode and disrupt the careful and truthful representation of benefits and risks that prescribers need to make appropriate judgments about drug use. Exaggeration of risk could discourage appropriate use of a beneficial drug. [37][13]

[12] quoting [4].
[13] *See* page 3935.

1. Organization of the safety information in a Product Label

FDA carefully controls the content of prescription drug labeling. Labeling is FDA's principal tool for educating healthcare practitioners about the risks and benefits of approved products to help ensure safe and effective use. [37]

The organization of a drug label is specified by regulation,[14] and has evolved over time. FDA determines whether the information provided is in the proper sections of the label, and assures that an approved label is balanced and accurate. Prior to 2006, warning information was organized in the safety section of the label as: a) Contraindications, b) Warnings, c) Precautions, and d) Adverse Reactions.[15]

"Warnings" describe serious adverse reactions and potential safety hazards, limitations in use imposed by them, and steps that should be taken if adverse reactions occur. In 2006, FDA clarified the distinction between the Adverse Reactions section and Warnings and Precautions sections to better define FDA labeling requirements. [37] As FDA stated, this was not a change in its position. Adverse Reactions require "some basis to believe there is a causal relationship."[16] Warnings and Precautions are required when there is "reasonable evidence of a causal association" although causation need not be proven.[17]

Warnings may be given extra emphasis by placing them in a "box" with a black line around the warning, or emphasized through the use of bold type. FDA has the sole authority to add a boxed warning and over its contents: "To ensure the significance of boxed warnings in drug labeling, they are permitted in labeling only when specifically required by the FDA." [4] FDA limits the use of these warnings to avoid overuse, which would ultimately dilute the warning's impact. FDA carefully reviews serious and fatal adverse effects of drugs and makes determinations when a boxed warning is necessary. Only those adverse events which are considered to be reasonably associated with the drug are to be included in the "Adverse Reactions" section of the labeling.

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[14] 21 CFR 201.57 and 21 CFR 201.80 enumerate labeling requirements for prescription drugs and spell out what must be included in each section of the labeling.

[15] In 2006, FDA eliminated the distinction between the Warning and Precautions section of the label to create a single section. FDA commented that based on physician surveys "the distinction between warnings and precautions is not meaningful to practitioners who use labeling." [37] Current labels may also describe safety determined from clinical trials in a "Clinical Trials" section, clinically relevant animal toxicity information in a "Nonclinical Toxicology" section, and spontaneous reports in a "Post-marketing" section. Transition to a reorganized labeling format began in 2006.

[16] 21 CFR 201.57(c)(7).

[17] 21 CFR 201.57(c)(6).

Although as a prescription product, the Mirena labeling is written in technical language for healthcare professionals, the prescribing information labeling also contains information for patients. One section of the Precautions section, entitled "Patient Counseling" describes information about risks and benefits for a healthcare provider to discuss with a patient. Additionally, in the FDA approved prescribing information, Mirena contains a "Patient Information" section, written in lay language to facilitate discussion between prescriber and patient.

In my experience at FDA, the process of changing safety labeling is usually initiated by the NDA sponsor, but FDA will also initiate safety labeling changes. The FDA review staff will conduct its own independent analysis of warnings and make determinations based on that analysis.

2. Changing Labels

FDA has the sole authority to approve products and their labels and the sole authority to remove such approval. While companies must submit labeling applications to FDA, and are responsible for labeling content, the New Drug divisions have the final word on labeling changes. Since passage of the Food Drug and Cosmetic Act in 1938, manufacturers are not permitted to sell a product when FDA determines that the labeling is "false and misleading" or that the drug lacks "adequate instructions for use."[18] To remain on the market, FDA requires such labels be changed to comply with the labeling regulations. Additionally, since 2007, FDA is required to notify holders of approved NDAs of new safety information it believes should be in the labeling and can order the NDA holder to implement necessary safety labeling changes.[19]

The regulations provide for two types of labeling change applications: those which require FDA's prior approval (Prior Approval Supplements, or PAS); or those which may be implemented immediately,[20] while the application is still pending (Changes Being Effected supplements, or CBE). Both PAS and CBE applications are subject to review and approval by

[18] Whether a drug's labeling is "false and misleading" requires consideration of, among other things, the totality of information provided in the labeling and available about the drug in general. Prescription drugs are exempt from "adequate instructions for use," which refers to nonprescription products, if the product complies with the FDA labeling regulations found at 21 CFR 201.57 and elsewhere.

[19] FDCA 505(o)(4).

[20] In the case of some moderate changes in manufacturing, the changes can be implemented 30 days after submission.

FDA. FDA's authority over boxed warnings, set forth in the regulations, makes clear that changes to boxed warnings cannot be made by CBE applications.[21]

Unless there is evidence of a causal association that satisfies the standard for inclusion in a label, the FDA will reject a CBE supplement implemented by a sponsor.[22] If FDA ultimately does not approve a CBE which has been implemented, the manufacturer must cease use of the CBE labeling and modify the labeling content to comply with FDA-approved language. Manufacturers are not permitted to sell products without approved labeling, and to do so may result in a finding that they are misbranded, subjecting the manufacturer to possible seizure of the product, substantial fines, criminal penalties, and/or NDA withdrawal.

In my experience, FDA expects prior approval review for substantive labeling changes, in particular, when the labeling change involves a safety issue already under review by FDA. For significant changes, it is helpful for companies and FDA to review together the scientific evidence that each brings to the understanding of a safety issue. A PAS provides an opportunity for such interaction. In some cases, when FDA is considering similar potential safety issues with multiple drugs, FDA may require that all of the products incorporate identically worded safety information.

III. Mirena (Levonorgestrel-Releasing Intrauterine System)

The importance of safe and reliable contraception is beyond question. Prevention of unintended pregnancies has significant health benefits. Even today, pregnancy complications include a not-insignificant risk of thromboembolism, cardiovascular disease, stroke, hemorrhage, infection and death. [69] Several major categories of contraceptives are widely available. Reversible drug and device contraception includes barrier methods, systemic hormonal products, and intrauterine devices (IUDs). [74]

The earliest IUDs for contraception were developed in the 1920's and were made out of silver, gold, silk, stainless steel and other materials, however, wide-scale use would await better acceptance of contraception following World War II and the introduction of plastic IUDs such as the Lippes Loop in 1962. [19][23] The complications associated with these IUDs included

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[21] *See* 21 CFR 201.80(e).
[22] 21 CFR 314.70(c)(7).
[23] *See also* https://medicine.buffalo.edu/research/research_highlights host.html/content/shared/smbs/research_highlights/lippes-loop.detail html.

increased menstrual bleeding, pain, expulsion, and less commonly, infection, ectopic pregnancy, embedment in the uterine wall, and perforation of the uterus.

Clinical acceptance of IUDs suffered a severe set-back in the 1970's, due to reports of serious infections associated with the Dalkon Shield, which used a unique braided string that allowed bacteria to ascend into the uterine cavity. Copper containing IUDs were first marketed in the late 1960's followed by development of progesterone eluting devices in 1976 that led to the design of Mirena. Historically, IUDs, including Mirena, have been more widely used outside of the United States and, as a result, applications for marketing approval in the U.S. have included reviews of both investigational and postmarketing studies, as well as pharmacovigilance results from other countries.

In actual use, IUDs are among the most effective forms of contraception, and one that avoids many of the adverse effects, some very serious, of systemic hormone contraception. In a 2009 policy report, the American College of Obstetricians and Gynecologists (ACOG) [48] recommended the use of IUDs as first-line contraception when a long-acting reversible form of contraception is indicated. IUDs are also recommended as first-line contraception for most women by the Centers for Disease Control and Prevention [51], World Health Organization [50], American Academy of Pediatrics [67], and ACOG [54]. ACOG specifically recommends Mirena for use in obese women, and the CDC recommends Mirena without restriction in this population. [40, 51] The Mayo Clinic's Department of Obstetrics & Gynecology similarly notes that (1) progestogen-only or non-hormonal contraceptives are "preferred methods of contraception for women who are obese," (2) that intrauterine devices are effective at preventing unintended pregnancies regardless of BMI, and (3) that intrauterine devices "may be the ideal first option" for women with elevated BMIs. [61]

Mirena's contraceptive benefit derives in part from Levonorgestrel (LNG). Levonorgestrel is the levo enantiomer of the progesterone norgestrel. It was first synthesized in the 1960's and has been used in contraceptives since the 1980's as an oral contraceptive, either alone or in combination with ethinylestradiol. LNG has also been used in contraceptive implant systems and in several IUDs. [20] Levonorgestrel is an active ingredient in 54 NDAs and ANDAs and is available over the counter for post-coital "emergency" contraception.[24] All of these dosage forms are included in the World Health Organization's list of essential medications. [75]

[24] The FDA Labeling database lists 75 separate product labels where levonorgestrel is an active ingredient. *See* https://rm2.scinet fda.gov/druglabel/#lblsums-1.

As a contraceptive, the benefit of Mirena in preventing unwanted pregnancies is considered against the adverse medical effects of pregnancy itself, which will be prevented by contraception. Pregnancy continues to be associated with significant, sometimes life-threatening complications, including thromboembolism, hypertension, gestational diabetes, hemorrhage, and infection. [62]

A. IND and NDA Approval

1. Population Council IND

On August 17, 1983, an IND was submitted[25] to FDA's Division of Metabolic and Endocrine Products Division by the Population Council, an international nonprofit organization headquartered in New York City that has conducted contraceptive research and developed a number of contraceptive products, including the copper T, Norplant, and Mirena. On December 12, 1983, FDA found that the safety and dose in the proposed clinical trial was supported by the IND and agreed that the trial could proceed.[26] Development of Mirena continued in world-wide trials, and Mirena was first approved for marketing in Finland in 1990. On November 12, 1997, the IND was transferred to Berlex Laboratories, who filed an NDA on January 21, 2000, based on the U.S. and world-wide experience with Mirena.

2. NDA Review and Approval

On January 21, 2000, Berlex Laboratories, Inc. submitted an NDA for Mirena. FDA approved the application on December 6, 2000, after a very interactive review that included 41 supplemental submissions.

The purpose of the NDA review is to determine if FDA can conclude that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the approved prescription labeling.[27] With each NDA supplement, FDA again reviews the evidence to this standard.

At the time of the NDA submission, Mirena had been approved and marketed in 28 countries, beginning in the early 1990's. In addition to containing more than 20 investigational trials and

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[25] *See* MIR_INDNDA_290033 to MIR_INDNDA_290974.
[26] *See* MIR_INDNDA_289748 to 9752.
[27] MIR_INDNDA_00010719 at 00010720.

the relevant medical literature, the U.S. NDA included the global marketing experience with Mirena. This data contributed years of postmarketing surveillance safety information.

Plaintiff's expert Dr. Ross criticizes the use of studies performed outside the U.S. to support the Mirena NDA and questions the adequacy of the sponsor's showing that foreign study results were applicable to the U.S. population and practice of medicine. Review of the basis for Mirena approval demonstrates that the studies included a subset that met the FDA clinical trial requirements for approval of a contraceptive product in the United States. Moreover, Dr. Ross offers no evidence that the populations studied were not susceptible to IIH. Ultimately, based on the fact that the FDA approved the NDA, the FDA reviewers must have concluded that these studies met the regulatory requirements.[28] I see no indication that they did not.

a. Effectiveness

The Integrated Summary of Efficacy (ISE) [21], provided adequate and well-controlled study evidence of effectiveness from 17 clinical trials, begun in 1981, with 1,594 women from qualified sites.[29] The studies randomized participants to the levonorgestrel-releasing intrauterine system, copper-containing IUDs, or oral contraceptives. Six hundred thirty-three women completed five years of study. In the pivotal trial, the Pearl Indices[30] at 5 years were 0.08 for levonorgestrel-releasing intrauterine systems and 1.26 for the copper IUD. As the NDA ISE reported: "At 5 years, the cumulative discontinuation rates/100 women for all sites were as follows: PID (1.6), expulsion (5.2), bleeding (10.7), pain (4.9), hormone related (11.2), amenorrhea (5.8), other medical (9.2), planning pregnancy (14.2), other personal (10.7), and other discontinuation (1.0)."[31]

b. Safety

The NDA's Integrated Summary of Safety (ISS) [22] included safety information from 3,021 women in 20 clinical trials, including 2,899 women from contraceptive studies, with the remainder from studies of menorrhagia and endometrial protection. The total safety database included the experience of 7,688 woman-years total exposure. The adverse events leading to discontinuation are described above, most commonly involving menstrual disorders. Five

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[28] *See* 21 CFR 314.106(b); MIR_HC_238038 at 238045.

[29] Site qualification was determined by adherence to specified good clinical practice requirements. There were 745 women studied in nonqualified sites which were not relied upon to determine efficacy.

[30] The Pearl Index is a statistical estimation of the number of unintended pregnancies in 100 woman-years of exposure.

[31] MIR_INDNDA_00127646 at 128220.

ectopic pregnancies occurred, with a Pearl Index of 0.07 at five years. No cases of IIH were reported.

FDA medical reviewer Dr. Furlong included in her analysis an examination of known adverse reactions of other levonorgestrel containing contraceptives. As she noted:

> Unlike other contraceptive methods containing levonorgestrel, the effectiveness of Mirena appears to depend more on the local than the serum concentration of levonorgestrel. In fact, the serum concentration of levonorgestrel produced by Mirena is lower than the serum concentration produced by any currently marketed levonorgestrel-containing contraceptive in the USA (e.g., approximately one tenth the serum concentration produced by an oral contraceptive containing 0.l mg levonorgestrel and about half that produced by the Norplant System). [24][32]

She further commented: ***"Recommended warnings include the warnings that are currently on the U.S. labels for the other two USA-approved IUDs.*** These include warnings about pelvic infection, ectopic pregnancy, congenital anomalies, septic abortion, perforation, embedment, and breast cancer."[24][33] (emphasis added). Although Bayer included the 1997 Norplant label as part of its Mirena NDA submission, Dr. Furlong did not conclude that the Mirena label should include Norplant's warnings, nor those of any of the oral contraceptive products containing levonorgestrel.[34]

The science supports Dr. Furlong's comment about the differences between Mirena and other LNG-containing contraceptives then on the market. Norplant releases approximately three to four times more LNG on a daily basis than does Mirena, and this LNG is released systemically.[35] Given its systemic effects, Norplant users have been found to have mean LNG blood concentrations almost double those of Mirena users.[36] The NDA review documents and subsequent labeling reviews show that FDA and Berlex Laboratories considered some safety labeling to be appropriate for all IUDs. FDA, however, did not take the same approach with

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[32] *See* page 7.

[33] *See* page 6.

[34] MIR_INDNDA_53366 at 55897.

[35] Norplant releases "85 mcg/day followed by a decline to about 50 mcg/day by 9 months and to about 35 mcg/day by 18 months with a further decline thereafter to about 30 mcg/day." [17] Compare this to Mirena, which releases "approximately 20 mcg/[day] over the first 3 months tested (day 0 to day 90). It is reduced to approximately 18 mcg/day after 1 year and then decreases progressively to approximately 10 mcg/day after 5 years." [65]

[36] Among Norplant patients, LNG levels are 327±119 pg/mL at 12 months, and 258±119 pg/mL at 60 months. [17] For Mirena patients, mean concentrations are 180±66 pg/mL at 12 months and 159±59 pg/mL at 60 months. [65] Since the daily dose of LNG decreases over time, Table 1 of Dr. Etminan's report, which compares the mean blood LNG level for Norplant users after one year to the mean blood LNG level for Mirena users between one and six months, is an inapt comparison.

Norplant. FDA did not require Mirena, a locally-acting LNG IUD product, to contain the same warnings as Norplant, a subcutaneous implant which releases approximately four times as much LNG directly into systemic circulation than Mirena.

IV. Idiopathic Intracranial Hypertension

Idiopathic intracranial hypertension[37] (IIH) refers to elevated intracranial pressure in the absence of an intracranial structural abnormality that could cause the increased pressure, and with normal cerebrospinal fluid (CSF). IIH most often presents in young women who are overweight or obese, although it is occasionally seen in children, men, and older adults as well. [52] Signs and symptoms include papilledema, headache, pulsatile noises, and visual disturbances.

Apart from IIH, other sources of elevated intracranial pressure include brain tumor or trauma, intra-cerebral hemorrhage, infection, venous thrombosis, hydrocephalus, and post-operative effects. Because these and other causes of elevated pressure must first be ruled out, IIH is a diagnosis of exclusion. The Clinical diagnosis is based on the modified Dandy criteria: [1, 57]

- Elevated intracranial pressure, but with normal CSF composition [46][38];
- Neuroimaging showing no etiology for intracranial hypertension;
- No other cause of intracranial hypertension apparent [71];
- No other neurologic abnormalities or impaired level of consciousness;
- Signs and symptoms of increased intracranial pressure (headache, transient visual obscurations, pulse synchronous tinnitus, papilledema, and/or visual loss).

IIH is a relatively rare condition, although it is significantly more common in several distinct population groups. In the general population, the incidence rate of IIH has been estimated at approximately 1 per 100,000 person-years. [7] Due to increases in obesity since those data were generated several decades ago, and because obesity dramatically increases the risk for IIH, the incidence rate is likely higher today. Among women of childbearing age,

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[37] Idiopathic intracranial hypertension is also known as “pseudotumor cerebri” and “benign intracranial hypertension.”

[38] Intracranial pressure between 20-30 mm Hg signals mild intracranial hypertension, levels between 20 and 25 mm Hg require treatment in most circumstances, and sustained pressures above 40 mm Hg indicate severe elevation. [46]

however, there is an estimated incidence rate of approximately 3.5 per 100,000 woman-years. [7] IIH is most common in a subset of these women: overweight and obese women of childbearing age. Among women of childbearing age, those who are overweight or obese develop IIH at a rate between approximately 14.85 per 100,000 woman-years (for women 10% or more over ideal body weight) and 19.3 per 100,000 woman-years (for women 20% or more over ideal body weight). [7] Women who have recently gained weight are also at increased risk of developing IIH. [39] Studies examining the body habitus of IIH patients have found that upwards of 94% of those patients were overweight or obese, and controlled studies consistently determine that excess weight and recent weight gain are independent risk factors for developing IIH. [7, 8, 10, 12, 31, 39, 42, 53, 55, 71] It is worth noting that obese women tend to have lower progesterone levels compared to non-obese women. [60]

With many patients, IIH either resolves spontaneously or resolves after the patient receives a lumbar puncture. [59] Lumbar puncture is a diagnostic tool which tests the pressure and composition of CSF, but it often provides symptom relief by removing fluid and reducing pressure. Apart from lumbar puncture, common treatments include acetazolamide, a diuretic which decreases CSF production, and recommending weight loss. [71] Acetazolamide and weight loss have each been shown to improve symptoms of IIH. [59, 64]

Other systemic diseases have been reported in association with IIH, as have certain vitamin deficiencies and excesses, but no causal relationship between IIH and these factors has been demonstrated. [42] Although IIH has also been reported in patients using the Norplant contraceptive system, as discussed below, these reports and the medical literature do not provide reasonable evidence of an association between Norplant and IIH, let alone reasonable evidence of a causal association between them.

A. The Norplant IIH Warning

Based on a small number of case reports, the following IIH warning was added to Norplant:[39]

> *Idiopathic intracranial Hypertension*
>
> Idiopathic intracranial hypertension (pseudotumor cerebri, benign intracranial hypertension) is a disorder of unknown etiology which is seen most commonly in obese females of reproductive age. There have been reports of idiopathic

[39] November 16, 1992 letter from Victoria to Sobel (response to FOIA #2015-8544) (confirming that Wyeth "would be submitting proposed labeling for Norplant to address spontaneous reports of Idiopathic intracranial hypertension which had been received for users of the Norplant System."); Record of November 10, 1992 Rarick conversation and November 15, 1992 letter (indicating the same).

> intracranial hypertension in NORPLANT SYSTEM users. A cardinal sign of idiopathic intracranial hypertension is papilledema; early symptoms may include headache (associated with a change in frequency, pattern, severity, or persistence; of particular importance are those headaches that are unremitting in nature) and visual disturbances. Patients with these symptoms, particularly obese patients or those with recent weight gain, should be screened for papilledema and, if present, the patient should be referred to a neurologist for further diagnosis and care.
>
> NORPLANT SYSTEM should be removed from patients experiencing this disorder. [17]

Norplant was also contraindicated in women with IIH.

I have seen no evidence that the Norplant IIH warning was based on anything more than spontaneous reports of IIH in Norplant users. Spontaneous adverse event reports can be useful in identifying potential signals for further investigation, but they also suffer from a number of deficiencies. As addressed in greater depth earlier in this report, adverse event reports cannot be used to calculate incidence rates or prove causal associations. Adding warnings based on spontaneous adverse event reports alone runs the risk of over-warning. Over time, FDA has become more acutely aware of the risk of over-warning. Labeling that conformed to the 1979 labeling standards [4] often included many warnings based on postmarketing reports that were no longer included in the labels for the same drugs after converting to the Physician's Labeling Rule (PLR) standard, first proposed in 2000 and in effect as of 2006. [25] In part, this related to an increased attention by FDA to over-warning, and importantly, an emphasis on the need for "reasonable evidence of a causal association" for a labeling Warning. [37] Norplant was withdrawn from the market prior to the PLR's passage. However, it is my opinion that the available evidence fails to provide reasonable evidence of an association between IIH and Norplant (i.e., evidence that IIH occurs more often in Norplant users that would be expected by chance alone).

1. The Norplant Medical Literature and Spontaneous Reports

The scant literature discussing IIH in Norplant users does not provide reasonable evidence of an association between Norplant and IIH.

In 1993, Sunku, A.J., et al. [11], reported two patients who developed IIH after having Norplant implanted. The authors discussed that the relationship between Norplant and IIH could have been "coincidental," and the publication lacks information about excess weight or recent weight gain, both of which are known risk factors for IIH. Such case reports provide no reasonable evidence of an association between Norplant and IIH.

In 1995, in a letter to the editor Alder, J.B., et al. [14], described two additional Norplant patients who developed IIH. Neither patient was obese, although the authors do not state whether the patients were overweight or had recent weight gain. Alder did not report whether the patients had Norplant removed but did report three recurrences of IIH in one patient. Alder also searched adverse event reports from three databases and identified 56 cases of "intracranial hypertension or disk edema" associated with Norplant. However, this is a broader group of disorders than IIH alone, as there are many causes of intracranial hypertension and disk edema, and Alder did not specify how many had IIH, or if clinical narratives were available for the cases from the databases. The authors commented: "Levonorgestrel may have contributed to the onset of intracranial hypertension, or it may have had nothing to do with it."

Wyeth-Ayerst responded to Alder's letter, presenting details about the company's 70 spontaneous reports. [15] Three-quarters of the IIH patients for whom weight information was available were obese, raising the issue of whether Norplant or obesity was associated with IIH. As Wyeth observed: "In 24 of the 44 reports in which information on follow-up was available, idiopathic intracranial hypertension did not abate after the implant was removed. This further confounds the issue of a causal relation." Overall, even assuming a conservative 20% discontinuation rate, Wyeth calculated an observed reporting rate of 4.1 per 100,000 woman-years. This is nearly five times less than the expected rate among obese women, who accounted for a substantial majority of the reports, and it is in line with the incidence rate among reproductive-age women generally.

With respect to Norplant-associated visual disturbances, a report by the National Academy of Sciences' Institute of Medicine commenting on the provisional final results from the International Collaborative Postmarketing Surveillance led by the World Health Organization in 1998 found no association between Norplant and visual disturbance. Although 15 of 19 cases of visual disturbance in this study were among Norplant users, closer scrutiny revealed no causal relationship between Norplant and visual disturbance. Six cases proved to be disorders of refraction, requiring eyeglasses; five cases were various diagnoses including borderline glaucoma, an intraocular foreign body, thyroiditis, cestode infection, and keratitis; and 8 cases (7 in Norplant users) were 1- to 3-month complaints associated with headache or fatigue, all reversible. [20][40]

[40] *See* page. 62.

In 1995, Wysowski, D.K., and L. Green [13] evaluated serious adverse reports in Norplant users from all sources available to FDA,[41] including 39 cases of IIH. In 21 cases no body weight information was available, but all patients whose weight was reported had recent weight gain (8 cases) and/or were obese (16 cases) or overweight (2 cases). Four patients continued using Norplant and the IIH resolved, as did 16 patients who had Norplant removed. Eight patients had Norplant removed but symptoms continued. The interpretation of dechallenge cases is made difficult by the concurrent treatment with lumbar puncture and acetazolamide.[59, 64] The authors estimated that the reporting rate was approximately 5.5 per 100,000 woman-years, which did not exceed the expected background rate for IIH. The authors concluded that it was not possible to determine whether Norplant or body habitus were related to the development of IIH.

Irvin Sivin of the Population Counsel responded to Wysowski and Green's calculation. [16] He pointed out that the authors had underestimated the years of experience American women had with Norplant, resulting in an over-estimate of the reporting rate by 34% to 50%. Using corrected data, Sivin determined that the IIH reporting rate was actually between 2.8 and 3.7 per 100,000 woman years. This rate was well within the background rate for women of childbearing age (approximately 3.5 per 100,000) and markedly below that for overweight or obese women (approximately 19.3 per 100,000). Sivin concluded that "the incidence of serious adverse events during Norplant use does not raise the 'suspicion of a causal association with Norplant." I agree with Sivin's conclusion.

I also note that when attempting to understand adverse event under-reporting and its impact on estimating incidence rates, it is not correct to assert that the extent of under-reporting is known, and that incidence can be arrived at by multiplying the known reports by some number, such as 10.

Studies have demonstrated that the extent of underreporting for adverse events varies widely by medication and even within a class of medications. One reference [35], cited by Dr. Ross, estimates that 15% of serious conditions are reported. Another well-documented study found a reporting rate of 35%. [45] There is no single under-reporting rate that applies to all drugs and all adverse reactions in all clinical settings. Reporting rates are influenced by factors including publicity received by a medicine, the background rate of the adverse event in the general population, and the time the product has been on the market. [45] As Hazell, L., and Shakir, S. A. [35] conclude "[i]t would be inappropriate to apply a standard 'correction factor' based on

[41] Wysowski and Green reviewed spontaneous reports from manufacturers, consumers, and health care professionals; clinical trials; and the medical literature.

the results of this study, since there is inevitably considerable variation in under-reporting for different drugs and types of ADRs, in different populations and at different points in time."

B. Other Levonorgestrel Containing Drugs and IIH Labeling

No LNG-containing product currently marketed in the United States carries an IIH warning. Neither the LNG-containing oral contraceptives nor the other LNG-containing IUDs marketed in the U.S. (Skyla and Liletta), which FDA approved after Bayer had shared the results of its signal assessments for IIH (discussed below), contain an IIH warning.[42] Also, Nexplanon, a progestin-containing implant approved in 2006, does not have an IIH warning.[43]

Although not marketed in the U.S., FDA did approve the Jadelle implant, which was the successor product to Norplant. The Jadelle prescribing information was also based on Norplant,[44] using the pre-PLR labeling standard that Norplant followed. As discussed above, the evidence did not support an association between Norplant and IIH, let alone a causal association, and I have seen no evidence that Jadelle is any different. In my opinion, the fact that Jadelle carries an IIH warning[45] does not justify including such a warning in the Mirena label.

C. The Adequacy of the Mirena Label with Respect to IIH

1. Initial Mirena Prescribing Information

At the time of Mirena's launch, clinical trial and post-marketing data did not support the inclusion of an IIH warning in the Mirena label. As described above, Berlex Laboratories' proposed labeling was based on a concise summary of the scientific evidence obtained from adequate and well controlled trials, the safety experience with Mirena, postmarketing surveillance, and the medical literature. [23] In my opinion the approved Warning labeling concisely summarized the known risks of Mirena so that a healthcare professional could consider the risks and benefits for individual patients. Those risks did not, and still do not include IIH.

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[42] https://dailymed nlm nih.gov/dailymed, 2013 Skyla Label, 2015 Liletta Label.
[43] 2006 Nexplanon Label, 2015 Nexplanon Label.
[44] Nov. 13–14, 2015 Dep. Tr. of Juliane Schoendorf, at 44:14–44:20, 79:6–79:10, 114:8–114:11, 148:11–148:15, 170:11–170:14.
[45] 2002 Jadelle Label.

By 2000, no clinical trial participants had been diagnosed with IIH during a Mirena trial. Bayer did report a single potential IIH case in the August 2000 PSUR,[46] before Mirena's initial U.S. label was finalized. However, this case did not provide adequate evidence of an association between Mirena and IIH. The patient had a history of IIH predating her Mirena usage, and the case report addressed the patient's worsened headache after receiving acetazolamide (a medication for which she had a known toxicity), but not symptoms while she was using Mirena.[47] The case report does not indicate that the patient's IIH recurred or worsened as a result of Mirena use. Although Dr. Ross criticizes Bayer for its handling of this IIH report, the FDA received the report months before issuing preliminary labeling comments in November 2000.[48] If FDA had believed that this case report was reasonable evidence of an association between Mirena and IIH, it was fully within FDA's authority to require an IIH warning prior to Mirena approval. The FDA did not require such a warning.

In my opinion, FDA's approach was reasonable. Although FDA's 2005 Guidance for Industry: Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment [33] states that "single well-documented case report" can create a signal "particularly if the report describes a positive rechallenge or if the event is extremely rare in the absence of drug use," that standard has not been met here. First, this case is not "well-documented," as the report lacks critical information (e.g., the patient's body habitus). Second, the report does not "describe[] a positive rechallenge." Third, although IIH is rare, it is not "extremely rare" without the use of Mirena.[49] There is a known background rate of IIH in women of childbearing age, and a significantly higher background rate among those with excess weight, or those with recent weight gain. Most importantly, the function of a signal is to highlight a potential safety concern for further evaluation, not to prompt an immediate change in labeling. Therefore, even if this case report were the type that could create a signal, it would not have triggered an obligation to add an IIH warning to Mirena's label without further investigation.

The November 2001 PSUR, which reported three additional cases of IIH among Mirena users, also did not justify the addition of an IIH warning to the label.[50] First, FDA received this PSUR and could have required action from Bayer if it believed action to be necessary. Second, it is notable that there had been just 4 spontaneous reports of IIH after use of Mirena by more than 2

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[46] PSUR's are the European periodic safety reports that FDA accepts in place of the U.S. PADER-format safety reports.
[47] MIR_INDNDA_00032125 at 32610.
[48] MIR_INDNDA_00010880.
[49] The example that FDA has historically given is agranulocytosis with thiouricil to treat hyperthyroidism, a extremely rare drug-event combination and an event unreported in association with thyroid disease.
[50] MIR_AC_00174527.

million women. Even accepting underreporting, this reporting rate is just a fraction of the expected incidence rate of IIH in women of childbearing age. Thus, it was reasonable for Bayer not to further investigate the link between Mirena and IIH or to seek FDA permission to modify its label.

Evidence suggests that by the time the Mirena label was being negotiated, FDA had become more alert to preventing over-warning than it had been earlier in the 1990s when Norplant added its IIH warning. For example, during Mirena label discussions, FDA struck Bayer's proposed warning about venous thromboembolism (VTE) that indicated based on epidemiologic studies of progestin-only pills that there may be a slight, non-statistically significant increase in risk of VTE.[51] This is an example that when FDA finds insufficient scientific justification to conclude that there is reasonable evidence of an association, FDA will not accept a Warning.

2. Postmarketing Safety Information and Pharmacovigilance

At all times since Mirena's approval in 2000, Bayer has maintained strong pharmacovigilance practices that provide accurate and timely evaluation and reporting of postmarketing safety data. Collecting and analyzing spontaneous postmarketing adverse event data is an important task, however, these reports cannot be used to assess causality. The FDA makes this clear on its website, which states that "[s]ubmission of a safety report does not constitute an admission that [a] . . . product caused or contributed to an event."[52] Instead, a positive signal suggests deeper investigation into the association between a medicine and an event is needed.

Three times since Mirena's approval – in 2008, 2014, and 2015 – Bayer has conducted signal assessments to determine whether the updated Mirena data warranted further investigation into the relationship between Mirena and IIH. These investigations occurred after the issuance of the PLR, under which a medication label must warn of an adverse event when there is "reasonable evidence of a *causal* association" between the medication and the event.[53] The FDA's 2005 Guidance [33] suggests considering the following factors when determining whether a causal relationship exists:

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[51] MIR_CCDS_00000742, MIR_INDNDA_00010880, MIR_JR_00095903, MIR_INDNDA_00044480.

[52] openFDA, *About*, FDA.gov (updated 3/10/16) ("Submission of a safety report does not constitute an admission that medical . . . product caused or contributed to the event. The information in these reports has not been scientifically or otherwise verified as to a cause and effect relationship and cannot be used to estimate the incidence of these events.").

[53] 21 CFR 314.125.

1. Occurrence of the adverse event in the expected time;
2. Absence of symptoms related to prior exposure;
3. Evidence of positive dechallenge or positive rechallenge;
4. Consistency of the event with the established pharmacological effects of the product;
5. Consistency of the event with the known effects of other products in the class;
6. Existence of other supporting evidence from preclinical studies, clinical trials, and/or pharmacoepidemiologic studies; and,
7. Absence of alternative explanations for the event – such as confounders.

As discussed in detail below, each of Bayer's three assessments appropriately concluded that there was not reasonable evidence of a causal association between Mirena and IIH, and that no further investigation was necessary. These assessments were shared with the FDA, which had the explicit authority to require the addition of safety language to product labels. FDA did not conclude from the signal assessments that there was reasonable evidence of a causal association between Mirena and IIH, thus did not require an IIH warning.

a. 2008 Signal Assessment

In 2008, because of several spontaneous adverse event reports of IIH among Mirena users, the British health authority, the MHRA, requested that Bayer conduct an investigation of IIH reports. Dr. Juliane Schoendorf of Global Pharmacovigilance led the investigation, and findings were reported in the 2008 PSUR.[54]

Bayer found no confirmed cases of IIH in clinical trials and no articles discussing IIH in Mirena patients. A database search for three terms – benign intracranial hypertension, intracranial pressure increased, and papilledema[55] – located 24 cases of diagnosed or suspected IIH. At this point, the estimated post-marketing experience with Mirena exceeded 33 million woman-years, with an estimated 12.76 million units sold. This resulted in a reporting frequency of 0.07 cases per 100,000 woman-years, based on a 10% annual discontinuation rate.[56] More than 80% of patients whose weight was reported were overweight or obese, which suggests that that weight,

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[54] MIR_AC-R_00178489-00178493.

[55] While it is reasonable to identify potential cases with broader terms such as papilledema, review of the narrative, usually not available from pharmacoepidemiology studies or most spontaneous report databases, is necessary to identify suspected IIH cases. Bayer reviewed the case reports and excluded from further consideration those that did not represent IIH.

[56] Recent studies of Mirena use have reported annual discontinuation rates of 11-12%. Moreau C. Frequency of discontinuation of contraceptive use: results from a French population-based cohort. Hum Reprod. 2009; 24(6):1387-1392; Peipert JF. Continuation and Satisfaction of Reversible Contraception. Obstet. Gynecol. 2011; 117(5):1105-1113.

the primary risk factor for IIH, played a role. Apart from weight, there were no discernible patterns in the relevant data. Some patients reported IIH symptoms prior to receiving Mirena, and in 3 of 8 cases where information was available, symptoms did not resolve after the Mirena was removed. There was no clear case of positive dechallenge, as those patients whose Mirenas were removed also generally underwent lumbar puncture as part of the diagnosis, as well as receiving other IIH treatments.

Given the incidence rate for IIH among women of childbearing age, a finding of 0.07 cases per 100,000 woman-years is extremely low, even assuming underreporting. Given the population that uses Mirena, and especially given the ACOG recommendation that Mirena be a preferred contraceptive option among obese women, one would expect to see *more* IIH among Mirena users than we do.

Overall, data from the 2008 signal assessment did not indicate that Mirena presented an increased risk of developing IIH. MHRA concurred with Bayer's assessment that there was "insufficient evidence of an association between Mirena and BIH,"[57] and agreed that Bayer was not obligated to undertake observational studies or add an IIH warning to Mirena's label. Bayer did agree to continue monitoring IIH adverse event reports.

b. 2014 Signal Assessment

Following the 2008 signal assessment, Bayer continued monitoring adverse event reports of IIH. In 2014 Bayer undertook another signal assessment after identifying an increase in IIH reporting resulting from reports generated from legal cases.[58]

Bayer's review of the epidemiology and medical literature confirmed that there was still no support in the studies for a connection between IIH and Mirena. An updated review of clinical trial data found three cases of potential IIH, none of which appeared to have been caused by Mirena:

- A patient with pre-existing IIH received Skyla, another LNG IUD. During her time with Skyla, "no worsening of the pseudotumor occurred."[59] Bayer appropriately concluded this was not a case of IIH related to Mirena or Skyla.
- A patient developed diplopia shortly after her Mirena insertion, although it was unclear whether she had IIH, and a lumbar puncture was never performed. Symptoms resolved

[57] MIR_JSEU_00780138.
[58] MIR_PKEU_00699321-00699335.
[59] MIR-JSEU_01446069.

without Mirena removal.[60] Bayer appropriately determined that the patient's symptoms were not related to her Mirena usage.

- An obese 37-year-old woman (BMI 31) had a second Mirena placed after 5 years with her first Mirena. Ten months later, after 5 years and 10 months of consecutive Mirena use, she developed IIH. The patient recovered without removing Mirena.[61] The investigator appropriately concluded that IIH was not related to Mirena, and Bayer concurred.

An updated review of adverse event reports found 66 reports of IIH, with a cumulative postmarketing experience of approximately 99.4 million woman-years. This resulted in a steady reporting rate of 0.07 per 100,000 woman-years, despite the surge in reports coming from legal claims, and demonstrates no increased risk of developing IIH among Mirena users.

A deeper look at the 66 cases reveals the same themes that have consistently appeared in analyses of IIH patients. There was no clear temporal pattern between insertion and development of IIH symptoms, with almost one-third of cases reporting symptom onset between years 2 and 11 of Mirena use, when LNG release levels would have decreased, and the other cases dispersed fairly equally over time. Where information was available, 81% of patients had excess weight or had experienced recent weight gain, the major risk factors for IIH.

Finally, there was no clear relationship between the presence of Mirena and IIH symptoms, as some patients recovered with Mirena still in place, there were no positive dechallenges, and some patients' symptoms did not improve after Mirena removal. Of those who did recover after Mirena removal and treatment for IIH, some did not experience improvement until several years after removal. This timeline demonstrates that an ongoing source of LNG did not cause the patients' IIH symptoms.

c. 2015 Signal Assessment

In 2015 Bayer conducted another signal assessment,[62] this time in response to a new publication by Etminan [76] which included a FAERS analysis suggesting a small increase in the risk of

[60] MIR-JSEU_01057343.
[61] MIR_BSR_36776; MIR_ISEU_268963.
[62] MIR_KCOPLEY_JSEU_00000046 to 00000067.

developing IIH with the use of Mirena.[63] Bayer studied the Etminan publication and another publication, a meeting abstract by Rai [72], and again queried its database for IIH reports.

Bayer was unable to recreate Etminan's disproportionality scores from his FAERS analysis. Instead, Bayer's search of the FAERS and WHO databases for IIH in Mirena users compared to all other female patients ages 17-45 found no disproportionate reporting of IIH among Mirena users. Having reviewed this analysis and the Etminan and Rai papers, I agree with Bayer's critical assessment of them. I will discuss the shortcomings of these papers in more detail in a later section of this report.

Finally, Bayer found 114 IIH cases reported for Mirena and 1 for Skyla (Jaydess), with a total postmarketing exposure of approximately 120 million woman-years. This resulted in an estimated reporting rate of 0.09 cases per 100,000 woman-years, a small increase over the 2014 findings. This is not surprising, given that 46 of the 114 reports stemmed from litigation. Again, even accounting for Dr. Ross's hypothesized reporting rate, this reporting rate is significantly lower than what would be expected from women of childbearing age, let alone an overweight or obese population. As has consistently been the case, the vast majority of women for whom body habitus data were available had excess weight, or had experienced recent weight gain. Additionally, there was no consistent period between Mirena insertion and symptom onset, and there were no clear cases of positive dechallenge. Nor were there any cases of rechallenge.

In sum, Bayer's signal analyses demonstrate that there is not reasonable evidence of an association, let alone a causal association, between IIH and Mirena. This is consistent with results from numerous studies finding no statistically significant relationship between the use of oral contraceptives and IIH. [6-9, 12]

D. Epidemiology Studies of Mirena and IIH

The medical literature regarding Mirena and IIH consists entirely of a single case report and two epidemiologic studies. Due to their flaws and inherent limitations, none of these sources provide any evidence of a causal association between Mirena and IIH.

[63] Etminan also conducted a retrospective cohort study which found no statistically significant difference in IIH risk between Mirena users and the users of two combined oral contraceptives.

1. Martinez (2010)

In 2010, H. Martinez reported a "very atypical case" of IIH in a woman who used an unspecified LNG IUD. [49] Although the case report indicates that the woman was not obese, it provides no information about whether the patient was overweight or had recent weight gain, both of which are independent risk factors for IIH. Nor does it indicate when IIH developed vis-à-vis insertion of the IUD. Although the patient's doctors recommended removal of her IUD, the case report does not indicate whether the IUD was ultimately removed. Even assuming that the IUD was removed, the patient was treated with acetazolamide, precluding any assessment about whether removal contributed to improvement in the patient's symptoms. [64] In short, this single case report provides no evidence of a causal association between Mirena and IIH.

2. Etminan (2015)

In 2015 Etminan, M., et al. [76] published a reporting disproportionality analysis of IIH and Mirena using the FAERS database and a retrospective cohort study. A closer review of this article reveals that Etminan's reported results have serious methodological flaws that limit the validity of the authors' conclusions.

First, with respect to both studies, Etminan uses incorrect search terms. Etminan searches the FAERS database for "benign intracranial hypertension, idiopathic intracranial hypertension, cerebral edema, intracranial hypertension, papilledema and papilledema [sic]." For the retrospective cohort study, Etminan searches for "obstructive hydrocephalus[,] idiopathic normal pressure hydrocephalus, benign intracranial hypertension, cerebral edema and papilledema." Cerebral edema (accumulation of excessive fluid within the brain tissue), idiopathic normal pressure hydrocephalus (enlargement of cerebral ventricles without evidence of chronic increased intracranial pressure), and obstructive hydrocephalus (blockage of the flow of cerebrospinal fluid out of the brain's ventricles), would each preclude a diagnosis of IIH under the modified Dandy criteria. [1, 57] Intracranial hypertension (high pressure inside the skull) is a general condition that can reflect numerous conditions other than *idiopathic* intracranial hypertension. Papilledema (swelling of the optic nerve due to increased intracranial pressure) can be present in any disorder that increases intracranial pressure.

Second, Etminan does not report any effort to verify the diagnoses coded in the FAERS database or in the IMS LifeLink database that was used for the retrospective cohort study. This important step is essential for interpretable pharmacoepidemiology studies. FDA generally recommends that sponsors of pharmacoepidemiologic studies "validate diagnostic findings through a detailed review of at least a sample of medical records." [33] Etminan's failure to do so here is

particularly troubling, given that the ICD-9 code for IIH has only a 55% positive predictive value. [66]

Third, neither the disproportionality analysis of reporting behavior, nor the retrospective cohort study contained any covariate information about the well-established risk factors of excess weight or recent weight gain, which is particularly important given the ACOG recommendations [40] discussed above regarding IUD contraception for obese women. This creates confounding by indication.

Fourth, although Etminan's disproportionality analysis purports to quantify the odds of reported cases of intracranial hypertension among Mirena users, Etminan does not report restricting his database search to women of reproductive age. Because incidence rates of IIH are substantially lower in men, children, and non–reproductive age women, including those populations in the comparison biases the results toward a higher odds ratio for Mirena use, which is of course a product only used by women of reproductive age.

Fifth, while Etminan purports to conduct Bayesian sensitivity analyses for both studies to estimate the effect of an unknown prior, the assumptions underlying these analyses are invalid, and the way he reports the results is misleading. With respect to his FAERS disproportionality analysis, Etminan adjusted the odds ratio "according to estimates in the medical literature" for the relationship between intracranial hypertension and Mirena (but not for the relationship between intracranial hypertension and weight). Yet Etminan cites no literature that would support using a prior of 1.5 to 2.5, which presupposes that there is a relationship between Mirena and IIH. I am not aware of any literature that would support such an assumption.

For the retrospective cohort study, Etminan adjusted the ratio according to estimates of the relationship (1) between excess weight and Mirena use, and (2) between excess weight and intracranial hypertension. Etminan selected symmetrical priors, which (1) assume that it is equally likely that overweight and obese women are attracted toward use of combined oral contraceptives as it is that they are attracted toward Mirena use, and (2) assume that obesity is just as likely to increase the risk for intracranial hypertension as it is that obesity decreases the risk for intracranial hypertension. Given that Mirena is recommended for obese women over combined oral contraceptives [40], and given that obesity is a known risk factor for IIH – facts that the publication even acknowledges, it is not valid to select symmetrical hypothesized odds ratios for these relationships. The "risk" of use of Mirena by obese women and the risk of obesity for IIH should both be greater than 1. By reporting the average effect of his symmetrical

priors Etminan has misleadingly showed that his Bayesian analysis will have no effect on his odds ratios.[64]

Sixth, in a 2016 letter to the editor, Friedman reports that Etminan had been retained as a medical expert for Plaintiffs in this litigation prior to publication of the article. [82] In his response, Etminan did not deny Friedman's allegations, instead insisting that the study was "independent" in spite of his "involvement as an expert in any litigation." [81] Etminan's failure to disclose this conflict of interest — Etminan went so far as to explicitly "declare no conflict of interest in preparing this article" — is of concern.

Despite the flawed methodology which would bias the results against Mirena, it is noteworthy that Etminan's retrospective cohort study reports no statistically significant difference in the risk of IIH between Mirena and either of two oral contraceptives (EE-norgestimate and EE-norethindrone). Etminan's assertions in the publication that "EE-norethindrone is protective for ICH" as compared to Mirena, and that there is a "higher risk of ICH for Mirena compared with EE-norgestimate," both of which are contradicted by the results of the cohort study, further reveal the biases of the authors.

3. Rai (2015)

In 2015, a meeting presentation abstract by Rai, R., et al. [72], was published with a half-page description of a purported case-control study. The methodology is flawed in numerous respects, rendering meaningless the reported results.

In selecting the case group, 473 patients with "ICD-9 codes for pseudotumor cerebri" were screened according to the study's inclusion criteria. Out of the 176 patients that met those criteria, 59 completed telephone birth control histories, and 8 reported having used Mirena for contraception at the time of IIH symptom onset. This methodology is problematic in several respects. First, while Rai reports using "ICD-9 codes for pseudotumor cerebri," Rai does not report which codes he used. Given that there is only one ICD-9 code for pseudotumor cerebri — "benign intracranial hypertension" — to the extent that Rai used multiple codes, he must have used codes that were over-inclusive or incorrect.[65] Second, the small percentage of patients who completed Rai's telephone interview raises concerns about selection and response bias. Third, Rai reports no effort to confirm the diagnosis of IIH in any of the patients in the case group,

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[64] *See* Table 1.

[65] *See* ICD-9-CM Diagnosis and Procedure Codes, *available at* https://www.cms.gov/medicare/coding/ICD9providerdiagnosticcodes/codes.html.

despite the fact that the ICD-9 code for IIH has been shown to have only a 55% positive predictive value for identifying patients. [66]

To select the control group, Rai queried CPT codes in a health claims database for LNG IUD insertion in 220,904 women without "ICD-9 codes for PTC" who were aged 18-55 and had at least one clinical encounter from 2008-2013. Rai identified 4,408 Mirena users (approximately 2.0% of women in the database). Again, methodology of the selection of controls is problematic. No telephone interviews were performed to verify whether or not any patients used Mirena. Given that IUD usage in the United States from 2008-2013 fluctuated between 3.8% and 7.2% of all reproductive-age women [70], it is likely that Rai underestimated the number of Mirena users in the control group, which would have the effect of overestimating the odds ratio. As Rai fails to identify the health claims database used to select the control subjects, it is difficult to analyze the control group further. Third, the fact that Rai selected cases and controls using distinct methodologies presents a serious risk of ascertainment bias. Fourth, Rai reports no attempt to match cases with controls beyond female gender and age.

The Rai abstract suffers from another major flaw: Excess weight and recent weight gain are strongly associated with an increased risk of IIH, yet Rai fails to control for those confounders. Although Rai reports that "[t]here were no significant differences between LNG-IUS users and non-users in terms of . . . body mass index [or] recent weight gain," this does not indicate that Rai controlled for excess weight or recent weight gain when calculating the presented odds ratio. Rather, this statement about BMI and weight gain is simply a comparison between the IIH patients who did use Mirena and the IIH patients who did not use Mirena. It is not a comparison between the IIH patients who did use Mirena and the non-IIH controls. Moreover, the Valenzuela abstract, which presents data from the same case-control study, reports that twice as many cases had recent weight gain than the control group. [73]

Given the numerous flaws in the Rai abstract, the reported odds ratio of 7.7 cannot be taken at face value. Indeed, the authors themselves recognize that the evidence is "preliminary," that the connection between Mirena and IIH is merely a "possib[ility]," and that removal of Mirena in a patient who develops IIH is generally not warranted.

V. Dr. David Ross's Report [80]

I disagree with Dr. Ross's assessment of the evidence for a relationship between Mirena and IIH and his conclusions about the need for a warning for IIH in the Mirena prescribing information

labeling. Dr. Ross asserts that the Mirena label is inadequate because it does not contain an IIH warning. Dr. Ross supports this argument in two major ways:

First, he focuses on the label for Norplant, a subcutaneous LNG implant withdrawn from the market more than a decade ago. Dr. Ross argues that Norplant's label, which contained language regarding IIH, should have guided development of the Mirena label, regardless of whether there was sufficient evidence of an association to support the language in Norplant's label and regardless of whether Mirena's own clinical trials and post-marketing data suggested an association between Mirena and IIH.

Second, he argues that Mirena's post-marketing data constituted reasonable evidence of a causal association between Mirena and IIH, and should have compelled the company to introduce an IIH warning. Neither claim is supported by the record.

A. Norplant Labeling Is Not an Appropriate Source for Mirena Labeling

Dr. Ross's claim that Mirena's launch label should have included an IIH warning drawn from Norplant's label is without support and contrary to the FDA's conclusion regarding the adequacy of Mirena's label at the time of FDA approval.

First, I disagree with Dr. Ross's conclusion that "the Norplant warning automatically created an association" between Mirena and IIH. FDA can — and does — impose common warnings on drugs in a pharmacological Class when FDA concludes that there is likely a Class effect. There is no indication in the Mirena FDA review documents, or in the labels that FDA approved, that FDA considered the Norplant labeling to be class labeling for all levonorgestrel products. In fact, to the contrary, FDA medical reviewer Dr. Furlong noted that "[u]nlike other contraceptive methods containing levonorgestrel, the effectiveness of Mirena appears to depend more on the local than the serum concentration of levonorgestrel" and ultimately recommended that Mirena "***include the warnings that are currently on the U.S. labels for the other two USA-approved IUDs***" [24][66] (emphasis added). These warnings did not include an IIH warning. [24][67] Internal communications demonstrate that the Mirena launch label was developed using FDA's suggested approach, ultimately modeling the Mirena label primarily on the labels for other IUDs, with the contents of the Norplant label being included only where there was scientific

[66] *See* page 7, and MIR_INDNDA_53366 at 55897.
[67] *See* page 6.

support for doing so.[68] Employing other IUD labels when drafting the Mirena label was a sensible approach, given (1) all three products are IUDs which work by affecting the uterine environment, and (2) the differences between Mirena and Norplant.

Second, Bayer faced no obligation to adopt the Norplant label language simply because the two systems each employed LNG. Dr. Ross cites no authority for his claim, and indeed manufacturers generally need not employ warnings from other medications. Bayer reasonably and appropriately decided that the Norplant label should be used only on a case-by-case basis when scientific evidence demonstrated its applicability to Mirena.[69] For example, the Norplant label included a precaution about autoimmune diseases related to silicone use. Bayer considered this precaution but determined that "[f]rom a medical/toxicological perspective there is no reason to assume that the silicone tubing of Mirena might induce autoimmune disease."[70] As a result, Bayer's proposed Mirena label did not include similar language about risks of silicone.

Third, Dr. Ross cites no authority for his claim that in the absence of clinical trial data disproving the hypothesis that Mirena causes IIH, Bayer was obligated to include an IIH warning in its label. Nor does he provide support for his claim that Bayer was obligated to conduct pivotal studies that were sufficiently powered to establish the safety of Mirena with respect to IIH. Given how rare IIH is in the population, it would have been impossible to design and execute a clinical trial large enough to study the issue.[71] The FDA acknowledges that clinical trials are "impractical in almost all cases when the event rates of concern are less common than 1:2000-3000," [33] and IIH is significantly less common than that, even among obese women, who are at the highest risk. I am unaware of any sponsor ever being obligated to do a study of adverse events expected to occur just once in every 33,000 person-years. Rather, the whole purpose of pharmacovigilance is to detect signals of potential adverse events occurring too infrequently to be observed during clinical trials. [33] Indeed, plaintiffs' expert Dr. Fraunfelder states: "[T]he study population required in order to detect a single case of PTC among potential Mirena users would be at least 90,910. Obviously, this is an impractical number of subjects for a pre-marketing study." Perhaps more importantly, Dr. Ross's proposed warning

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[68] MIR_JR_00186051, MIR_JR_00186066, MIR_JR_00186596, MIR_JR_00186491, MIR_JR_00186518, MIR_JR_442929, MIR_PSEU_00530579.

[69] MIR_JR_00186491.

[70] MIR_JR_442929.

[71] Dr. Ross inaccurately states: "Reliable detection of a single case of IIH would require a safety database of 10,000 patients or more" [80], yet he cites a background rate of IIH as 3.3 per 100,000. A study of at least 90,000 patients would be required to have a 95% chance of detecting a single case. [43, 47]. This is just one of many errors and miscalculations in his report.

standard — inclusion of all theoretical adverse events in a label absent evidence disproving an association — would result in widespread over-warning, which presents two distinct risks. First, a label that contains numerous warnings not supported by medical evidence could dilute the importance of well-supported warnings.[72] Second, patients and their physicians may be deterred from using a highly efficacious and safe product if faced with a long list of warnings and precautions that are not based on rigorous scientific assessment.[73]

Fourth, Dr. Ross's criticism of Bayer for not having a procedure to evaluate headaches among clinical trial patients to see whether they were indicative of papilledema or other signs or symptoms of IIH is entirely unsupported. Headaches not only have a high background rate in the general population, but are also an extremely common and non-specific adverse event for many medications. It would be untenable to design a program that would include a diagnostic evaluation for IIH with each reported headache.

B. The Criticisms of the Bayer Signal Assessments Are Unfounded

Dr. Ross offers a host of minor and unfounded criticisms of the 2014 signal assessment with which I disagree:

- Dr. Ross concludes that Bayer failed to "address whether the risk of weight gain in Mirena users . . . could lead to obesity and thereby raise the risk of IIH." This criticism is without merit, as there is no evidence that Mirena causes significant weight gain. To the contrary, prospective studies have demonstrated minimal weight gain with Mirena use. [63]

- Dr. Ross claims that Bayer applied a "nonexistent regulatory standard" in concluding that "confirmed evidence for a causal association of levonorgestrel implant use and intracranial hypertension is lacking." He ignores Bayer's statement in the same

[72] *See* [4] ("The Commissioner believes that including theoretical hazards as contraindications in drug labeling would cause that very important section of the labeling to lose its significance."), [37] ("Overwarning, just like underwarning, can . . . have a negative effect on patient safety and public health. . . . FDA believes that including relative or hypothetical hazards diminishes the usefulness of the [contraindications] section."), [44] ("[I]nclusion of speculative or hypothetical risks, could . . . decrease the usefulness and accessibility of important information by diluting or obscuring it. As FDA has stated, labeling that includes theoretical hazards not well-grounded in scientific evidence can cause meaningful risk information to lose its significance.").

[73] *See* [44] ("[I]nclusion of speculative or hypothetical risks, could discourage appropriate use of a beneficial drug, biologic, or medical device . . . .").

paragraph that "available data for Mirena do currently not indicate that Mirena use would be associated with an increased risk for developing IIH."[74]

- Dr. Ross claims that Bayer focused "primarily on the potential alternative explanation of obesity as the cause for these cases," and, as a result, that Bayer's analysis "was directed at excluding a relationship between Mirena and IIH, rather than an objective exploration of the data." This criticism is unwarranted. Bayer examined whether there was a causal relationship between Mirena and IIH by looking for features that would suggest a causal relationship (e.g., common duration of onset, positive dechallenge, and the absence of alternative explanations), just as recommended by FDA's 2005 Guidance (sponsors should "look for features that may suggest a causal relationship between the use of a product and the adverse events"). [33][75]

- Dr. Ross claims that Bayer's Standard Operating Procedures for signal detection failed to require Bayer to submit its findings to FDA, but he ignores the fact that Bayer submitted each of its signal assessments to FDA as part of its PSURs.[76] Additionally, the FDA "will make its own assessment of the potential safety risk posed by the signal in question, taking into account all the information provided by the sponsor and any additional relevant information known to FDA (e.g., information on other products in the same class)." [33][77] FDA received Bayer's signal assessments and, having approved an IIH warning in the Norplant label years before, did not ask Bayer to add an IIH warning to the Mirena label. Nor was Bayer obligated to take additional steps after completing its signal analyses and finding no signal, apart from ongoing monitoring for future signals. FDA's 2005 Guidance clearly states that "risk management is an iterative process and steps to further investigate a potential safety risk, assess the product's benefit-risk balance, and implement risk minimization tools would best occur in a logical sequence, not simultaneously. Not all steps may be recommended, depending on the results of earlier steps." [33][78]

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[74] MIR_PKEU_00699321 at 00699334.
[75] *See* page 6.
[76] MIR_INDNDA_00246210, MIR_INDNDA_00340337.
[77] *See* page 18.
[78] Id.

C. The Epidemiology Evidence Does Not Support a Casual Association Between Mirena and IIH

Dr. Ross conducts his own disproportionality analysis of the U.S. adverse event data and suggests that Bayer should have compared reported adverse events for Mirena patients with IIH (22, by his count) against those reported for ParaGard (0) and other IUDs on the market (1). I fundamentally disagree with this approach, as FDA's 2005 Guidance notes that comparison between two or more reporting rates must be made with "extreme caution." [33] Additionally, when Dr. Ross conducted his review of the adverse event reports compiled in OpenVigil 2.0, he gathered the data incorrectly. Dr. Ross reported 22 unique reports of IIH in U.S. patients exposed to Mirena, when in fact there are only 14 unique cases of IIH.[79] In effect, Dr. Ross double-counted some patients, for whom multiple reports were submitted, and thereby overstated the number of cases of IIH observed in Mirena users by more than 50%. It is also notable that, where reported, the mean patient weight among the 14 patients was approximately 218 pounds (median 195.1 pounds), meaning that most of the patients were overweight or obese.

Moreover, the method Dr. Ross cites for his disproportionality analysis [27], the PRR, is not a method that FDA recommends for use with FAERS data when, as here, the total number of events is less than 20. [33][80] Dr. Ross even misinterprets the meaning of the PRR statistic when he comments that "the magnitude of this increase [in the PRR] indicat[es] that Mirena is likely related to IIH by accepted criteria." The PRR only shows differences in reporting rates and is not used to indicate that a drug and an event are "related."

Dr. Ross also attempts to compare Mirena IIH reporting to Skyla, Liletta, and ParaGard. Even when "extreme caution" is exercised, comparisons to other products can only be done if there is an adequate marketing period for products to generate results, which is not the case for the recently marketed Skyla (2013) and Liletta (2015). OpenFDA contains no adverse event reports associated with Liletta and just 1,430 adverse event reports associated with Skyla (compared to 73,330 adverse event reports associated with Mirena).[81] It is also not appropriate to draw conclusions from comparisons to older products such ParaGard, which was approved in 1984,

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[79] An Individual Safety Report (ISR) code is assigned to each unique report. A case ID is assigned to each unique patient. Where multiple reports are submitted for the same patient, multiple ISRs will be generated, but all of them will have the same case ID. There are only 14 unique case IDs associated with IIH among Mirena users in OpenVigil 2.0. *See* http://www.is.informatik.uni-kiel.de/pvt/OpenVigil/search/.

[80] *See* page 9.

[81] *See* http://www researchae.com/.

well before the implementation of the MedWatch program in 1992. While postmarketing reporting did occur before 1992, the number of reports submitted was just a fraction of the number of reports seen in more recent times. [45] Products that have long been on the market also tend to have very low reporting rates. Consequently, openFDA contains just 2,266 adverse event reports associated with ParaGard. Even more importantly, analyses of reporting rates in FAERS cannot provide information about incidence or prevalence of drug-associated adverse events. Such estimates must come from other sources, such as epidemiology studies for rare events.

Finally, Dr. Ross misquotes a sponsor's requirements. In FDA's 2005 Guidance, FDA explicitly does not require the use of data mining signal detection activities. [33][82] The cornerstone of pharmacovigilance systems is the case-by-case evaluation of individual reports and the submission of those reports in either 15-day or periodic reports.

Dr. Ross uncritically accepts the 2015 Rai abstract as evidence of "patients exposed to Mirena being 7.7 times more likely to develop IIH than non-users." Because the abstract has not been turned into a full-length article, the only information available about the study's methodology is what appears in half a page.

Dr. Ross uncritically accepts Etminan 2015 as evidence that "independent of potential confounders such as obesity, Mirena use increases the risk of IIH," a conclusion that even Dr. Etminan fails to draw from his own study in his own report.

VI. Dr. Mayhar Etminan's Report [78]

Dr. Etminan has offered an expert report in this litigation, and I take this opportunity to address several of his points.

A. Disproportionality Analyses

In Tables 2 and 3 of his report, Dr. Etminan lists the results of flawed disproportionality analyses using the FAERS and WHO databases. In Table 2, Dr. Etminan searched the FAERS database using OpenVigil 2.1 for cases of papilledema and IIH. In Table 3, he searched the WHO database for papilledema and "Hypertension intracranial."[83] Dr. Etminan's

[82] *See* page 9.
[83] "Who Analysis.xls"

disproportionality analyses for papilledema are irrelevant to whether there is a signal for IIH, as papilledema is not unique to IIH. And although "Hypertension intracranial" is the WHO Adverse Reaction Terminology (WHO-ART) term for IIH, it is also the WHO-ART term for fontanelle bulging and any other source of increased intracranial pressure.[84] Dr. Etminan did not review the case reports in an effort to discern how many cases of "Hypertension intracranial" represent IIH specifically.

With respect to Dr. Etminan's disproportionality analyses, Dr. Etminan purports to calculate reporting odds ratios from the FAERS and WHO databases for "common intrauterine contraceptives." Table 2 presents the FAERS results for Cu-7, Mirena, Depo-Provera, and all drugs containing levonorgestrel. Table 3 presents the WHO results for those same drugs, as well as ParaGard and Norplant. Dr. Etminan's comparator products are inappropriate. Cu-7, a copper IUD, was removed from the market in 1986.[85] Since the FAERS database includes data only from January 1, 2004 through June 30, 2014, one would not expect to see any reports of IIH in users of Cu-7. In fact, there are only 3 total adverse event reports for Cu-7 in the entire FAERS database.[86] Dr. Etminan also provides no explanation for why his search of "common intrauterine contraceptives" includes Depo-Provera (which is not an IUD, and which involves a different progestin than Mirena), Norplant (which is not an IUD), or all levonorgestrel-based products (which includes oral contraceptives). Depo-Provera is also uninformative due to the fact that there are only 4,734 total adverse event reports associated with it in OpenVigil 2.1 (compared to 68,150 reports associated with Mirena). These figures indicate that Depo-Provera is not a valid comparator product for Mirena, particularly for low frequency events like IIH.

Nonetheless, I attempted to reproduce Dr. Etminan's FAERS disproportionality analysis using OpenVigil 2.1, and the results that Dr. Etminan reports are incorrect. Dr. Etminan claims that there were 58 "Reported Cases" of IIH in Mirena users. While 58 unique reports were submitted (as evidenced by 58 unique ICR codes), multiple reports were submitted for several patients, such that only 40 unique cases are present in the database (as evidenced by 40 unique case IDs). Twenty-four of those cases occurred in the United States. Moreover, analysis of the individual case reports is inconsistent with a causal relationship between Mirena and IIH. Information on weight was available for 9 patients, with a mean weight of 206.5 pounds (median 198.4 pounds). The fact that weight information was not available for 31 patients further highlights the limitations of drawing conclusions from FAERS searches. There was also no common duration

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[84] *See* http://bioportal.bioontology.org/ontologies/WHO-ART?p=classes&conceptid=http%3A%2F%2Fpurl.bioontology.org%2Fontology%2FWHO%2F0115.

[85] Lewin T, Searle, assailing lawsuits, halts U.S. sales of intrauterine devices. NY Times. 1986.

[86] *See* http://www.is.informatik.uni-kiel.de/pvt/OpenVigil2.1/search.

between insertion of Mirena and onset of IIH. One patient's IIH reportedly pre-dated Mirena insertion by 13 days, one patient reportedly developed IIH on the same date as Mirena insertion, and the remaining 15 patients for whom information was available developed IIH between 5 days and 11 years after Mirena insertion, with no discernible pattern.

The biggest problem with Tables 2 and 3 is Dr. Etminan's conclusion that the results of his disproportionality analysis "allude to a causal link with LNG contraceptives, including Mirena, and IIH." Disproportionality assessments are merely measures of reporting behavior and do not assess risk or causality. The proper use of disproportionality measures is to identify signals of potential associations between drugs and adverse events that merit further study with reliable epidemiologic methods. As FDA's 2005 Guidance states, "[d]ata mining is not a tool for establishing causal attributions between products and adverse events," and measures of disproportionality "are inherently exploratory or hypothesis generating." [33] I do not find Dr. Etminan's disproportionality methods reliable or compelling.

B. Meta-Analyses

Dr. Etminan's Table 4, which reports a pooled odds ratio for IIH from four studies, is also incorrect. Dr. Etminan's meta-analysis pools the results of three oral contraceptive studies with the odds ratio reported by the Rai abstract. [72] None of the three oral contraceptive studies reported a statistically significant odds ratio. [8, 9, 12] In other words, the statistical significance of the pooled odds ratio is driven *entirely* by the odds ratio reported by Rai, which is flawed for the numerous reasons that I discuss above. Dr. Etminan provides no rationale for estimating the risk of Mirena by pooling the Rai odds ratio with odds ratios from studies of oral contraceptives.

Moreover, Dr. Etminan calculated the results of his meta-analysis using a fixed-effects model, rather than a random-effects model. A fixed-effects model assumes that the true effect size for all studies is identical, and that the only reason for variation between the studies is sampling error. By contrast, under the random-effects model, the goal is to estimate the mean of a distribution of different effects. Consequently, a random-effects model produces a similar pooled odds ratio but results in wider confidence intervals. Here, Dr. Etminan pools the results from studies that have different designs and that assess different contraceptive forms (oral contraceptives vs. IUDs). Dr. Etminan's choice of a fixed-effects model is not appropriate, as there is no scientific basis to assume that these very different hormonal products would have the same risk as Mirena. Simple inspection the of the data shows three oral contraceptive studies that have an average risk very close to the null, and a single study of a different product, Mirena, with a different risk estimate. In my opinion, there is no basis for including these four

studies together in a meta-analysis, and certainly no basis for assuming that they all model the same effect and differ only due to chance. Dr. Etminan also calculated the pooled odds ratio using a random-effects model (although he did not disclose the results in his initial report), and the result was an odds ratio that was not statistically significant (OR 2.08 (0.72-5.99)).[87]

Finally, Table 4 uses the wrong odds ratio from the Ireland study. Dr. Etminan uses the odds ratio for oral contraceptive use at least 12 months prior to diagnosis of IIH (2.50). Ireland separately reported the odds ratio for oral contraceptive use immediately prior to diagnosis (1.80). [8] Dr. Etminan should have used the latter odds ratio, which more accurately measures whether IIH was caused by oral contraceptive use. Had he done so, the pooled odds ratio would have decreased accordingly.

C. Reanalysis of the Rai Abstract

Acknowledging that the Rai abstract did not control for BMI or recent weight gain, Dr. Etminan purports in Table 5 to test the robustness of Rai's odds ratio using "hypothetical BMI values." However, the assumptions underlying this calculation are inaccurate. First, Dr. Etminan assumes, without justification, an odds ratio of 2 to 4 for the degree of confounding between BMI and IIH. Yet Daniels reported odds ratios of 6.5 for women with BMIs between 25 and 29, 19.5 for women with BMIs between 30 and 35, and 26.0 for women with BMIs above 35. [42] In other words, Dr. Etminan markedly underestimates the degree of confounding between BMI and IIH. Second, Dr. Etminan assumes that no more than 50% of Mirena users who developed IIH in the Rai study were overweight or obese. Given that excess weight has been shown to be present in much higher percentages among patients who developed IIH [12, 29, 31, 32, 73], this assumption cannot be justified. Thus, Table 5 does not adequately correct for the Rai abstract's failure to control for BMI or recent weight gain. In any event, modeling results based on such a small number of events cannot produce reliable results.

D. Dr. Etminan's Bradford Hill Analysis

Dr. Etminan concludes that there is a causal link between Mirena and IIH by misapplying the criteria introduced by Sir Austin Bradford Hill in 1965. [2] At the outset, it bears emphasizing that Bradford Hill envisioned applying his framework only *after* an "association between two variables" was "perfectly clear-cut and beyond what we would care to attribute to the play of chance." For the reasons that I discuss above, such an association between IIH and Mirena has

[87] "Response to Queries.pdf"

never existed. Therefore, it is inappropriate to even apply Bradford Hill's framework here. Even if it were appropriate to apply Bradford Hill, there is nothing about Bradford Hill that will salvage low quality evidence. In fact, what evidence there is struggles to meet the criteria for a signal, let alone provide evidence of a causal association.

Nonetheless, Dr. Etminan claims that a temporal relationship is present because "all women who experienced IIH or PE [sic] with Mirena mentioned in this litigation, the case report and the two epidemiologic studies [of] IIH and PPE were reported after a woman was exposed to Mirena." Yet among the criteria for inclusion in Dr. Etminan's study was use of "a study drug for at least six months before experiencing an event." [81] Similarly, Rai conducted telephone interviews of those patients with ICD-9 codes for IIH to obtain "birth control histories of the 3 month timeframe *preceding* IIH onset" and found 8 cases of IIH. [72] In other words, the designs of the studies excluded any cases without a temporal relationship. More importantly, this criterion asks more than the simple question of whether use of a drug preceded onset of an event. Rather, it asks whether the passage of time between use of a drug and onset of an event is consistent across cases. As Bayer's signal assessments have shown, and as my search of the FAERS database has confirmed, such consistency is lacking here. The only indisputable observation is that a few plaintiffs and reporters have concluded that a drug taken before an adverse event caused that adverse event.

Dr. Etminan states that the strength and consistency of the association have been shown by the disproportionality analyses from Tables 2 and 3, and the odds ratio reported by Rai. As discussed above, methodological flaws preclude reliance on any of these sources.

Dr. Etminan also asserts that the criterion of a dose-response relationship is irrelevant here because Mirena "comes as a fixed dose." Not so. For one, the amount of LNG released by a Mirena IUD decreases over time. [65] Dr. Etminan could have measured, but did not, whether IIH onset is more common shortly after insertion than toward the end of the five-year period. Moreover, since Mirena, Skyla, Liletta, and the various oral contraceptives that contain LNG are all associated with different mean serum blood concentrations of LNG, Dr. Etminan could have measured, but did not, whether incidence rates of IIH are higher among users of drugs associated with higher mean serum blood levels.

Dr. Etminan states that there is coherence and biological plausibility because contraceptive hormones "increase blood pressure and clotting." His theories are not supported by the literature. ACOG specifically states that Mirena is an "appropriate option in women with hypertension" because progestin has not been shown to significantly impact blood pressure.

[40] Moreover, a recent meta-analysis of eight observational studies calculated an odds ratio for venous thromboembolism (clots in the veins) among Mirena users of 0.61 (0.24 to 1.53). [56]

Dr. Etminan maintains that an analogy exists in that progestins other than LNG have been linked to IIH. Specifically, Dr. Etminan cites two case reports among users of medroxyprogesterone (MPA). [5, 41] In at least one case, the patient was overweight (BMI 28). [41] Regardless, two reports of IIH among MPA users are insufficient to establish an association.

Dr. Etminan acknowledges that specificity does not exist in this case but claims, without explanation, that this criterion "does not apply to this question." Although diseases can be caused by more than one mechanism, the absence of specificity nonetheless factors against a finding of causation.

Dr. Etminan asserts that there is experimental evidence of an increased risk of IIH with Mirena, based on "case-reports, disproportional analysis and epidemiologic studies." None of these are sources of experimental evidence.

Finally, Dr. Etminan states that there is dechallenge, which is not a Bradford Hill criterion, because (1) a single woman using MPA allegedly experienced resolution of IIH upon stopping use of the drug; (2) some women allegedly saw resolution of symptoms upon removal of Norplant; and (3) there is one "possible case [of dechallenge] with an intrauterine device similar to Mirena." However, MPA is an entirely different progestin than LNG. An unspecified number of the Norplant users who experienced resolution of symptoms were treated with lumbar punctures and/or acetazolamide [13], precluding any conclusion about whether Norplant removal or these therapies was the cause of their improvements.[59, 64] And as for the "possible case [of dechallenge] with an intrauterine device similar to Mirena," the author states that removal of the IUD was recommended by the patient's doctors, but does not indicate whether the patient followed that advice. [49] The patient was also treated with acetazolamide.

VII. Dr. Frederick Fraunfelder's Report [79]

Lastly, I briefly address the expert report that Dr. Fraunfelder submitted in connection with this litigation.

Dr. Fraunfelder opines that the cohort analysis performed in the 2015 Etminan article [76] "could suggest a possible class effect" because "the risk of PTC was similar to norgestimate, while norethindrone had a lower risk associated with use." The Etminan cohort analysis cannot be read as evidence of a class effect. For one, it is incorrect to state that norethindrone was

associated with a lower risk for IIH than Mirena, since the results of the cohort analysis were not statistically significant (OR 0.31 (0.04-2.29)). Moreover, given that every study that has assessed the risk of IIH among combined oral contraceptive users has found no increased risk [5, 6, 7, 8, 11], the fact that the risk of IIH among Mirena users was comparable to the risk among users of two combined oral contraceptives is evidence that Mirena does not cause IIH.

Dr. Fraunfelder also asserts that there are 105 reports in the National Registry of Drug-Induced Ocular Side Effects of "Benign intracranial hypertension, Papillodema, Intracranial pressure increased, and Optic nerve disorder." Out of those search terms, only "Benign intracranial hypertension" is specific to IIH. Because Dr. Fraunfelder has yet to provide the adverse event reports contained in the registry, I have been unable to determine how many of the reports are specific to IIH or to further analyze them (e.g., to determine how many of the women were overweight or obese). I note, however, that the registry collects adverse event reports from the WHO and FAERS databases, so many of the reports are likely duplicate entries for reports contained elsewhere. Dr. Fraunfelder notes that 5 out of 12 patients for whom dechallenge data was provided saw no resolution of symptoms upon removal of Mirena, which suggests that Mirena was not the cause of their IIH.

Finally, Dr. Fraunfelder recently added Exhibit A to his expert report, which contains the results of a search of the WHO database that is not referenced in his report.[88] While the search revealed 63 cases of various eye disorders among Mirena users, only 16 cases of IIH were located. Fourteen of those cases came from the United States. Since the WHO database includes adverse events reported to FAERS, only two new cases of IIH were located. The WHO database does not maintain data on weight, precluding an assessment of the number of women who were overweight or obese. No instances of positive dechallenge were located, and time between insertion of Mirena and development of IIH ranged from 5 to 1065 days, with no discernible pattern, making a causal relationship unlikely.

VIII. Principle Conclusions

In addition to the opinions expressed in the above report and based on the evidence presented, I conclude that:

1.) There has never been a confirmed safety signal related to IIH among Mirena users;

[88] "Fraunfelder-A(1) - WHO Data.pdf"; "Fraunfelder-A(2) - 5.30.2013 WHO Data SS.xlsx"

2.) Bayer's extensive pharmacovigilance efforts have carefully assessed clinical trial safety data, spontaneous adverse event reports, literature case reports, and published literature and have properly concluded that there is no reasonable evidence of an association between Mirena and IIH;

3.) The evidence for an association between Norplant and IIH is lacking, but in any case the Norplant warning is not an appropriate basis to warn about IIH in the Mirena labeling;

4.) Disproportionality studies do not show a statistically significant relationship between Mirena and IIH, but in any case are only evidence of a signal, not evidence of a causal association; and

5.) The Mirena label has always been adequate with respect to IIH. There has never been reasonable evidence of an association, causal or otherwise, between Mirena and IIH.

I reserve the right to supplement this report as new facts come to light, as the state of the science may change, or in response to the reports or testimony of other experts in this case.

[redacted]

David William Feigal, Jr. MD MPH March 24, 2016

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